# Cancer and Pathology

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**Abstract:** Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This is the literature collections on cancer and pathology reserches.
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## 1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

## Literatures

Albanell, J., X. Andreu, et al. (2009). "Guidelines for HER2 testing in breast cancer: a national consensus of the Spanish Society of Pathology (SEAP) and the Spanish Society of Medical Oncology (SEOM)." Clin Transl Oncol **11**(6): 363-75.

Identifying breast cancers with HER2 overexpression or amplification is critical as these usually imply the use of HER2-targeted therapies. DNA (amplification) and protein (overexpression) HER2 abnormalities usually occur simultaneously and both in situ hybridisation and immunohistochemistry may be accurate methods for the evaluation of these abnormalities. However, recent studies, including those conducted by the Association for Quality Assurance of the Spanish Society of Pathology, as well as the experience of a number of HER2 testing National Reference Centres have suggested the existence of serious reproducibility issues with both techniques. To address this issue, a joint committee from the Spanish Society of Pathology (SEAP) and the Spanish Society of Medical Oncology (SEOM) was established to review the HER2 testing guidelines. Consensus recommendations are based not only on the panellists' experience, but also on previous consensus guidelines from several countries, including the USA, the UK and Canada. These guidelines include the minimal requirements that pathology departments should fulfil in order to guarantee proper HER2 testing in breast cancer. Pathology laboratories not fulfilling these standards should make an effort to meet them and, until then, are highly encouraged to submit to reference laboratories breast cancer samples for which HER2 determination has clinical implications for the patients.

Anderson, T. J., J. Lamb, et al. (1991). "Comparative pathology of breast cancer in a randomised trial of screening." Br J Cancer **64**(1): 108-13.

In the Edinburgh Randomised Breast Screening Project (EBSP) to December 1988 there were 500 cancers in the study population invited to screening and 340 cancers identified in the control population. The size and negative lymph node status characteristics of invasive cancers from the two populations were significantly different (P less than 0.05). The cancers detected by screening were predominantly 'early stage', with 16% noninvasive (PTIS) and 42% invasive stage I (pT1 node negative), whereas cancers were frequently 'late stage' (more than pT2) and inoperable in nonattenders (44%) and controls (36%). Grouped according to customary size ranges of invasive cancers, the proportion of cases lymph node positive differed in those screen detected compared with controls, but the benefit in favour of screen detection was not constant. In comparisons of cancers detected at prevalence and incidence screens, as a test of conformity with screening theory, no significant differences were apparent according to size and lymph node status, yet the characteristics of histological type of cancer discriminated significantly (P less than 0.05). When these same histological characteristics were used to compare survival, the

capacity to separate invasive cancers into two groups having good and poor survival probabilities was evident, with a significant improvement for the screen detected poor survival group compared with controls (P less than 0.05).

Apple, S. K. (2006). "Variability in gross and microscopic pathology reporting in excisional biopsies of breast cancer tissue." Breast J **12**(2): 145-9.

Accurate and complete information in pathology reporting is essential since most breast cancer treatment decisions are based on pathologic findings. The College of American Pathologists (CAP) has guidelines for breast cancer reporting; however, pathology reports remain variable. Data were collected on 91 consecutive breast cancer excisional biopsies from "outside slide review" (OSR) cases for a 2-year period to determine the variability in pathology reports in gross and microscopic examinations from 50 different outside community and university hospitals located primarily in the southwestern United States. From the gross pathology report, the following items were analyzed: measurement and weight of specimens, orientation provided by surgeons, number of blocks submitted, designation of margins, and whether margins were indicated as "shaved" or "perpendicular" in relation to the breast tissue at the time of grossing. From the final diagnoses, the following items were analyzed: type and size of tumor, and surgical margins. The results show that 100% of the reports documented the measurement of specimen size, and 30% documented the specimen weight. Surgeons provided orientation of the breast specimens in 65% of cases. Surgical margins were inked in 58%, while only 18% described how margins were submitted (either shaved or perpendicular to the mass). Only 30% of specimens were submitted in toto, 1% were submitted with an unknown amount of tissue, and 69% were submitted in representative sections with an average of 13 blocks for lumpectomies. In the final diagnoses, all reports had documentation of the tumor type and size of the invasive cancer; 26% of the final diagnoses had ductal carcinoma in situ (DCIS) and just 5% of those reports documented the size of the DCIS. The surgical margin status was reported in only 76% of the final diagnoses. This study shows that the pathology reports were heterogeneous with respect to reporting gross and microscopic final diagnoses from the variable hospitals.

Armes, J. E. and D. J. Venter (2002). "The pathology of inherited breast cancer." Pathology **34**(4): 309-14.

Familial breast cancer has been recognised for many years. In the 1990s the genetic mechanism of inheritance of a proportion of these familial cancers was found to be attributable to germline mutation in either of two newly discovered genes, namely BRCA1 and BRCA2. Since the discovery of these genes, studies have been performed in which the pathological characteristics of familial cancers arising in patients with germline BRCA1 and BRCA2 mutation have been examined. A distinct pathological phenotype of high-grade, oestrogen receptor-negative breast cancer, often with medullary features, has been consistently described for BRCA1 cancers. A less distinct phenotype has been described for BRCA2 cancers. The discovery of genotype-phenotype correlation has significant implications for patient management and novel treatment strategies, not only for inherited cancers, but for breast cancer in general.

Ashok, B. T., K. Tadi, et al. (2006). "Pre-clinical toxicology and pathology of 9-(2'-hydroxyethylamino)-4-methyl-1-nitroacridine (C-1748), a novel anti-cancer agent in male Beagle dogs." Life Sci **79**(14): 1334-42.

We have developed a group of 4-substituted-1-nitroacridines with potent anti-tumor activity against prostate cancer and less toxic than parent 1-nitroacridines. The most active 9-(2'-hydroxyethylamino)-4-methyl-1-nitroacridine (C-1748) was selected for pre-clinical studies. The current study was undertaken to evaluate clinical and/or morphological adverse effects of C-1748 as a single intravenous dose at concentrations ranging from 0.16 to 4.6 mg/kg administered to male Beagle dogs. The maximum tolerated dose was 1.5 mg/kg. Emesis was observed in all groups lasting an average of 30 min to 12 h post-dosing. At high dose, extreme aggression was observed in one dog followed by disorientation and depression lasting for 48 h a frequent observation with chemotherapy. Reductions in platelets and white blood cells were observed which was similar to that seen with other chemotherapeutic agents. A compensatory hyperplasia of lymph nodes and a transient and limited extravasation in the intestinal mucosa were also observed. Increases in aspartate aminotransferase, alkaline phosphatase and creatine phosphokinase were transient with normal levels restored by day 9. These enzyme increases were accompanied by epithelial hypertrophy of larger bile ductules in the periportal triads of the liver. The low toxicity profile and high tumor target activity make this novel class of drug a promising chemotherapeutic agent.

Bakheet, S. M. and M. M. Hammami (1994). "False-positive radioiodine whole-body scan in thyroid cancer patients due to unrelated pathology." Clin Nucl Med **19**(4): 325-9.

Radioiodine whole-body scanning is the imaging modality of the highest accuracy in diagnosing metastases from differentiated thyroid cancer. However, unrelated pathology in one of several nonthyroidal tissues that normally take-up/secrete radioiodine may result in a false positive scan. The authors report cases of an ectopic kidney, chronic sinusitis, dacryocystitis, and an artificial eye, complicating differentiated thyroid cancer, that on radioiodine scanning mimicked lumbar, frontal, and left and right orbital bone metastases, respectively. The nature of the radioiodine uptake was suspected from the results of a bone scan and proven by ultrasound (ectopic kidney), by reimaging after specific treatment (chronic sinusitis, and dacryocystitis), or by postwashing reimaging (artificial eye). To our knowledge, this is the first report of such cases. Nonthyroidal pathology should be excluded before exposing patients with apparent thyroid cancer metastases that have atypical characteristics on radioiodine whole body imaging.

Barbera-Guillem, E., M. B. Nelson, et al. (2000). "B lymphocyte pathology in human colorectal cancer. Experimental and clinical therapeutic effects of partial B cell depletion." Cancer Immunol Immunother **48**(10): 541-9.

Accumulating data are showing that the humoral immune response against tumors could favor tumor progression. However, no B lymphocyte pathology has been reported in cancer. Using anti-IgM Ab we nonspecifically depleted B cells in tumor-bearing mice, a treatment that resulted in significant reduction of tumor burden. We analyzed the B lymphocyte phenotype of abdominal lymph nodes and peripheral blood from advanced colon cancer patients by flow cytometry, and compared the B cell phenotype with that found in samples from normal donors. In both lymph nodes and peripheral blood of cancer patients, abnormal populations of B lymphocytes appeared that express an increased CD21 and/or sTn antigens on their cell surface. All patients showed a reduction of CD19+ cells. In a limited clinical test, we analyzed the effects of a partial B cell depletion with Rituximab. The treated patients did not develop any side-effects; the CD21-hyperpositive lymphocytes were reduced, but the proportion of sTn-positive lymphocytes remained unaffected. Apparent reduction of the tumor burden was reported in 50% of the patients when the treatment was ended.

Barocas, D. A., S. G. Patel, et al. (2009). "Outcomes of patients undergoing radical cystoprostatectomy for bladder cancer with prostatic involvement on final pathology." BJU Int **104**(8): 1091-7.

OBJECTIVE: To evaluate the impact of prostatic urothelial carcinoma (PUC) on survival of patients with bladder cancer undergoing radical cystoprostatectomy (RCP). PATIENTS AND METHODS: From 1998 to 2005, 463 consecutive RCPs were performed for UC of the bladder. Patients with PUC at final pathology were grouped by route of prostatic invasion (bladder origin or prostatic urethral origin) and by depth of invasion (carcinoma in situ, ductal invasion, and stromal invasion). Univariate and multivariate survival analyses were performed. RESULTS: In all, 35% (162/463) of patients had PUC. The 3-year overall survival (OS) was 58.2% for patients who did not have PUC, 59.2%, 51.7%, and 16.8% in order of increasing depth of prostatic invasion for patients with PUC of urethral origin, and 6.7% for patients with bladder-origin PUC. Survival differed significantly between stromal and non-stromal PUC ($P < 0.001$). Patients with PUC of bladder origin had a higher rate of positive lymph nodes (LNs) than patients with stromal PUC of prostate origin (74.3% vs 27.8%, $P < 0.001$), but survival was similar ($P = 0.619$). On multivariate analysis, age ($P = 0.035$), increasing bladder stage ($P = 0.003$), stromal invasion ($P = 0.002$) and positive LNs ($P < 0.001$) were predictors of poor OS. CONCLUSION: Depth of prostatic invasion correlates with outcome. While prostatic involvement originating in the bladder is associated with higher rates of positive LNs, survival is similar to patients with stromal involvement of urethral origin. Age, bladder tumour stage, prostatic stromal involvement and positive LNs predict adverse outcome. Our data support separate staging of the prostate in RCP specimens.

Biglia, N., L. Sgro, et al. (2005). "The influence of hormone replacement therapy on the pathology of breast cancer." Eur J Surg Oncol **31**(5): 467-72.

AIM OF THE STUDY: To assess whether the pathological characteristics of breast carcinomas arising in post-menopausal women who ever used hormonal replacement therapy (HRT) differ from those of post-menopausal patients who never used HRT. MATERIALS AND METHODS: Six hundred and forty three consecutive breast cancer patients were entered in a case control-study. Cases were represented by 111 breast cancer patients who had used or were using HRT at the time of diagnosis, while the remaining 532 patients who never used HRT were chosen as controls. RESULTS: Tumour diameter was smaller in HRT users (17.6 vs 22.1 mm; p=0.002) and tumours of lobular histology were almost twice more frequent among HRT users as in 'never users' (21 vs 12%; p=0.01). No differences were found in grading, hormonal receptor status and axillary nodal

status. The expression of c-erb B-2, p53, Ki67 and PS2 measured by immunohistochemistry was similar in the two groups. CONCLUSIONS: Our findings suggest that HRT use may modify the pathological presentation of breast cancer. Further studies are indicated, while other clinical-pathological characteristics did not differ according to HRT use.

Bjugn, R., B. Casati, et al. (2008). "Structured electronic template for histopathology reports on colorectal carcinomas: a joint project by the Cancer Registry of Norway and the Norwegian Society for Pathology." Hum Pathol **39**(3): 359-67.

Both individual patient treatment and cancer registries depend on adequate histopathology reports. To ensure the quality of these reports, professional organizations have published guidelines on minimum data sets for various cancer types. Norway has a population of 4.6 million, and all individuals have a unique identification number. As required by law, relevant information on cancer is submitted to the Cancer Registry of Norway. A closed, national health data network has been established facilitating electronic transferal between various institutions. The Cancer Registry and the Norwegian Society for Pathology have jointly established a nationwide project to (i) develop standardized templates in database format for histopathology reports on cancer resection specimens and (ii) develop an Extensible Markup Language (XML) standard to facilitate future electronic transfer of cancer reports from hospitals to the Cancer Registry. A minimum data set template for reporting colorectal carcinoma resection specimens and the Extensible Markup Language standard have been established. The template is based on international guidelines and classification systems. For most key parameters, pull-down menus with predefined alternatives have been constructed. The template is fully integrated into software being used by all pathology laboratories in Norway. Since the introduction of the template in April 2005, the template had been used for reporting 430 (93%) of 462 colorectal resections at 2 pilot laboratories (Akershus University Hospital [Lorenskog, Norway] and Stavanger, University Hospital [Stavanger, Norway]), demonstrating that high and consistent quality can be ascertained. Pathologists have found the template both time saving and user friendly. The template is now gradually implemented nationwide.

Blumencranz, P., P. W. Whitworth, et al. (2007). "Scientific Impact Recognition Award. Sentinel node staging for breast cancer: intraoperative molecular pathology overcomes conventional histologic sampling errors." Am J Surg **194**(4): 426-32.

BACKGROUND: When sentinel node dissection reveals breast cancer metastasis, completion axillary lymph node dissection is ideally performed during the same operation. Intraoperative histologic techniques have low and variable sensitivity. A new intraoperative molecular assay (GeneSearch BLN Assay; Veridex, LLC, Warren, NJ) was evaluated to determine its efficiency in identifying significant sentinel lymph node metastases (>.2 mm). METHODS: Positive or negative BLN Assay results generated from fresh 2-mm node slabs were compared with results from conventional histologic evaluation of adjacent fixed tissue slabs. RESULTS: In a prospective study of 416 patients at 11 clinical sites, the assay detected 98% of metastases >2 mm and 88% of metastasis greater >.2 mm, results superior to frozen section. Micrometastases were less frequently detected (57%) and assay positive results in nodes found negative by histology were rare (4%). CONCLUSIONS: The BLN Assay is properly calibrated for use as a stand alone intraoperative molecular test.

Bolster, M. J., P. Bult, et al. (2006). "Differences in sentinel lymph node pathology protocols lead to differences in surgical strategy in breast cancer patients." Ann Surg Oncol **13**(11): 1466-73.

BACKGROUND: Internationally, there is no consensus on the pathology protocol to be used to examine the sentinel lymph node (SN). At present, therefore, various hospitals use different SN pathology protocols of which the effect has not been fully elucidated. We hypothesized that differences between hospitals in SN pathology protocols affect subsequent surgical treatment strategies. METHODS: Patients from four hospitals (A-D) were prospectively registered when they underwent an SN biopsy. In hospitals A, B, and C, three levels of the SN were examined pathologically, whereas in hospital D, at least seven additional levels were examined. In the absence of apparent metastases with hematoxylin and eosin examination, immunohistochemical examination was performed in all four hospitals. RESULTS: In total, 541 eligible patients were included. In hospital D, more patients were diagnosed with a positive SN ($P < .001$) as compared with hospitals A, B, and C, mainly because of increased detection of isolated tumor cells. This led to more completion axillary lymph node dissections in hospital D (66.3% of patients ($P < .0001$), compared with 29.0% in hospitals A, B, and C combined). Positive non-SNs were detected in 13.9% of patients in hospital D, compared with 9.7% in hospitals A, B, and C ($P = .70$). That is, in 52.4% of patients in hospital D, a negative completion axillary lymph node dissection was performed, compared with 19.3% of patients in

hospitals A, B, and C combined. CONCLUSIONS: Differences in SN pathology protocols between hospitals do have a substantial effect on SN findings and subsequent surgical treatment strategies. Whether ultrastaging and, thus, additional surgery can offer better survival remains to be determined.

Bonney, W. W., A. R. Schned, et al. (1998). "Neoadjuvant androgen ablation for localized prostatic cancer: pathology methods, surgical end points and meta-analysis of randomized trials." J Urol **160**(5): 1754-60.

PURPOSE: At least 7 centers or collaborative groups have performed randomized clinical trials of neoadjuvant androgen ablation and radical prostatectomy versus radical prostatectomy alone for localized prostatic cancer. Our objectives were to analyze treatment results in terms of 2 standard outcome measures, to identify patient characteristics and other factors that explain outcome differences between trials, and to use pooled data to test the hypothesis that neoadjuvant treatment alters outcomes. MATERIALS AND METHODS: Trials were identified by MEDLINE search and review of published bibliographies, and examined for pathological techniques used to assign surgical end points. An attempt was made to contact trial group members for clarification and updated information. The resulting data were transformed as needed into standardized end points of pT stage and negative surgical margin. A series of contingency tables were used to study relationships between treatment outcomes and various risk factors. RESULTS: In addition to neoadjuvant treatment, numerous risk factors related to treatment regimen and patient characteristics apparently influenced treatment outcome, and should be reanalyzed when future followup trial data become available. CONCLUSIONS: In radical prostatectomy there is a need for uniform ways to process specimens, assign surgical stage and establish standardized surgical end points. Despite differences in risk factors, the trials were similar in overall design. Within these constraints neoadjuvant androgen ablation was significantly associated with low pT stage and negative surgical margin. Longer followup is needed to validate these measures as good surrogates for tumor specific survival.

Bono, A. V., F. Pagano, et al. (2001). "Effect of complete androgen blockade on pathologic stage and resection margin status of prostate cancer: progress pathology report of the Italian PROSIT study." Urology **57**(1): 117-21.

OBJECTIVES: To compare the pathologic stage and surgical margin status in patients undergoing either immediate radical prostatectomy or surgery preceded by 3 or 6 months of neoadjuvant hormonal treatment (NHT) in a prospective, randomized study. METHODS: Four hundred thirty-one men with prostate cancer were enrolled in the Italian randomized prospective PROSIT study. The whole-mount sectioning technique was used. By May 1999, the reviewing pathologist had evaluated 303 specimens. One hundred seven patients were untreated before radical prostatectomy was performed, and 114 and 82 patients had been treated for 3 and 6 months, respectively, with complete androgen blockade. RESULTS: Pathologic organ-confined disease was found in 63.1% of patients with clinical Stage B disease treated with 6 months of NHT versus 61.0% after 3 months of NHT and 37.5% after immediate surgery. Among patients with clinical Stage C tumors, pathologic staging found organ-confined disease in 62.5%, 32.1%, and 11.1% of patients after 6 months of NHT, 3 months of NHT, and immediate surgery, respectively. Three months of NHT produced a significant increase in negative margins both in patients with clinical Stage B and C disease, but the addition of another 3 months of treatment did not significantly improve this result. A lower degree of benefit was observed in patients with clinical Stage C tumors. CONCLUSIONS: This study shows that complete androgen blockade before surgery is beneficial in men with clinical Stage B disease. The effects are more pronounced after 6 months of NHT than after 3 months.

Bosman, F. T. (1999). "Molecular pathology of colorectal cancer." Cytogenet Cell Genet **86**(2): 112-7.

The identification of several types of familial colorectal cancer has led to the discovery of some of the genes involved in these diseases. It was subsequently shown that somatic mutations of these genes (APC, mismatch repair genes, TP53, KRAS, and DCC) also occur in sporadic colorectal cancer. Gradually, this molecular information is being incorporated into the standard histopathological analysis of colorectal cancer and can be used for the characterization of primary tumors. Although attempts have been made to use molecular parameters to better define dysplasia grades, differentiate between adenoma and carcinoma, and subtype carcinomas, histological parameters remain the standard for the classification of primary tumors. Nonetheless, molecular parameters may help define subgroups of colorectal carcinoma differing in prognosis and requiring individualized treatment regimens. Interesting possibilities are predicting the response to chemotherapy or radiotherapy at a molecular level and the search for metastasis by looking for molecular markers in lymph nodes or circulating blood. Other

pathological tests being developed include the detection of KRAS, TP53, or APC mutations in stool and plasma. Such approaches will have a significant impact on the clinical management of colorectal cancer.

Bostwick, D. G. (1994). "Prostate-specific antigen. Current role in diagnostic pathology of prostate cancer." Am J Clin Pathol **102**(4 Suppl 1): S31-7.

Prostate-specific antigen is the most important, accurate, and clinically useful biochemical marker in the prostate. It is manufactured by the secretory epithelial cells and drains into the ductal system, where it catalyzes the liquefaction of the seminal coagulum after ejaculation. Serum levels are normally less than 4 ng/mL (monoclonal) but vary according to patient age and race; any process that disrupts the normal architecture of the prostate allows diffusion of prostate-specific antigen into the stroma and microvasculature. Elevated serum prostate-specific antigen levels are seen with prostatitis, infarcts, hyperplasia, and transiently after biopsy, but the most clinically important increases are seen with prostatic adenocarcinoma. Cancer produces less prostate-specific antigen per cell than benign epithelium, but the greater number of malignant cells and the stromal disruption associated with cancer account for the increased serum prostate-specific antigen level. Serum prostate-specific antigen level correlates positively with clinical stage, tumor volume, histologic grade, and the presence of capsular perforation and seminal vesicle invasion; despite these strong correlations, its value is limited in predicting stage for individual patients. It may also predict the presence of lymph node metastases, bone metastases, and survival after androgen-deprivation therapy. The use of prostate-specific antigen has resulted in an increase in the early detection rate of cancer, and it is now advocated for annual routine use in men older than 40 years who are at increased risk and in all men older than 50 years. It is a test with high sensitivity and specificity that is rapid, inexpensive, minimally invasive, and acceptable to patients. In addition to serum prostate-specific antigen level, five derivatives of serum prostate-specific antigen were recently described that may increase the predictive value by accounting for confounding variables such as patient age, prostate volume, and cancer volume: age-specific reference ranges, prostate-specific antigen density, prostate-specific antigen velocity, prostate-specific antigen cancer density, and prostate-specific antigen doubling times. Serum prostate-specific antigen detects a heterogeneous group of cancers (clinical stage T1c) that are clinically important and potentially curable. Immunohistochemical expression of prostate-specific antigen in tissue sections allows determination of the prostatic origin of some metastatic adenocarcinomas, although extraprostatic expression of prostate-specific antigen has been reported in several tissues and tumors, including periurethral gland adenocarcinoma in women, rectal carcinoid, and extramammary Paget disease.(ABSTRACT TRUNCATED AT 400 WORDS)

Bostwick, D. G., J. Qian, et al. (2004). "Does finasteride alter the pathology of the prostate and cancer grading?" Clin Prostate Cancer **2**(4): 228-35.

All forms of androgen-deprivation therapy, including finasteride, induce distinctive histologic changes in benign and neoplastic prostatic epithelial cells, including cytoplasmic clearing, nuclear and nucleolar shrinkage, and chromatin condensation. Treated cancer has a significantly higher architectural (Gleason) grade, lower nuclear grade, and smaller nucleolar diameter than untreated controls, creating the potential for grading bias. Recognition of these changes may be difficult in needle biopsies and lymph node metastases with treated cancer because of the subtle infiltrative pattern and inconspicuous nucleoli. The effects of finasteride may be less pronounced than other forms of therapy with variable distribution throughout the prostate; further, there may be greater sensitivity of low and intermediate-grade cancer than high-grade cancer. The Gleason grading system for cancer should not be used after finasteride treatment as it is not validated in this setting and is likely to overestimate the biologic potential of high-grade cancer observed after therapy. Chemoprevention trials with agents such as finasteride that alter morphology should not rely on cancer grading as a secondary endpoint owing to grading bias.

Bostwick, D. G., J. Qian, et al. (2003). "Contemporary pathology of prostate cancer." Urol Clin North Am **30**(2): 181-207.

In less than 20 years since the introduction of serum PSA and the spring-loaded 18-gauge prostatic biopsy needle, pathologists have adjusted to the limited tissue requirements of narrow needle specimens to apply criteria for diagnosis and grading of prostate cancer, borrowing from lessons learned from radical prostatectomies. Substantial gains have been made during this period in the understanding of precancerous lesions, mimics of malignancy, the criteria for minimal cancer, variants of cancer, and treatment-induced changes. The light microscopic findings remain the criterion standard for diagnosis against which all new techniques should be measured. Numerous findings have proven to be of value, including simple quantitation of histopathologic

features, cancer volume, perineural invasion, and others.

Brennan, C. T., D. G. Sessions, et al. (1991). "Surgical pathology of cancer of the oral cavity and oropharynx." Laryngoscope **101**(11): 1175-97.

A study was designed to determine the influence of certain surgical pathologic findings on tumor spread and survival in patients with cancer of the oral cavity and oropharynx. All patients with the histopathological diagnosis of carcinoma of the oral cavity or oropharynx from 1955 to 1983 were included in the study. Using the Head and Neck Tumor Registry of the department of otolaryngology of the Washington University School of Medicine, information was obtained regarding preoperative evaluation, staging, classification, diagnosis, treatment, surgical pathology parameters, and outcome results. The patient populations consisted of 545 patients with oral cavity cancer and 224 patients with oropharynx cancer, all of whom were eligible for 3-year follow-up. Information from a retrospective analysis of the pretreatment examination records regarding site and size of the primary tumor and neck dissection, and specific treatment, and from surgical pathology reports regarding site, size, tumor spread and resection margins, was correlated with treatment outcome. The database file was analyzed using dbase III and its companion program Framework, and SAS PC (Statistical Analysis Systems for personal computers).

Bull, A. D., A. H. Biffin, et al. (1997). "Colorectal cancer pathology reporting: a regional audit." J Clin Pathol **50**(2): 138-42.

AIMS: To audit the information content of pathology reports of colorectal cancer specimens in one National Health Service region. METHODS: All reports of colorectal cancer resection specimens from the 17 NHS histopathology laboratories in Wales during 1993 were evaluated against: (a) standards previously agreed as desirable by pathologists in Wales; and (b) standards considered to be the minimum required for informed patient management. RESULTS: 1242 reports were audited. There was notable variation in the performance of different laboratories and in the completeness of reporting of individual items of information. While many items were generally well reported, only 51.5% (640/ 1242) of rectal cancer reports contained a statement on the completeness of excision at the circumferential resection margin and only 30% (373/1242) of all reports stated the number of involved lymph nodes. All of the previously agreed items were contained in only 11.3% (140/1242) of reports on colonic tumours and 4.0% (40/1242) of reports on rectal tumours. Seventy eight per cent (969/1242) of colonic carcinoma reports and 46.6% (579/ 1242) of rectal carcinoma reports met the minimum standards. CONCLUSIONS: The informational content of many routine pathology reports on colorectal cancer resection specimens is inadequate for quality patient management, for ensuring a clinically effective cancer service through audit, and for cancer registration. Template proforma reporting using nationally agreed standards is recommended as a remedy for this, along with improved education, review of laboratory practices in the light of current knowledge, and further motivation of pathologists through their involvement in multidisciplinary cancer management teams.

Carcangiu, M. L. (1997). "Uterine pathology in tamoxifen-treated patients with breast cancer." Anat Pathol **2**: 53-70.

In the last 20 years, tamoxifen has become the drug of choice in the treatment of breast carcinoma in both advanced and early stages. Furthermore, the ability of tamoxifen to prevent mammary carcinoma in the contralateral breast has prompted the creation of trials that include healthy patients with an increased risk of developing breast cancer with the purpose of verifying the drug's prophylactic action. As a consequence, a large number of healthy women or women with a long life expectancy are being treated with tamoxifen for long periods, making it crucial to study the possible long-term effects associated with this therapy. A weak estrogen-like effect of tamoxifen on the endometrium has been documented. This is supported by the increased incidence of glandular hyperplasia, polyps, carcinoma, and sarcoma in tamoxifen-treated patients. Some studies have shown that not all endometrial carcinomas arising in tamoxifen-treated patients have the favorable histologic and prognostic features typical of estrogen-associated endometrial cancers. This, in conjunction with the demonstrated carcinogenicity of tamoxifen in some animal models, indicates the need for caution in the use of this drug and makes strict gynecologic surveillance of tamoxifen-treated patients imperative.

Cavanna, L., R. Berte, et al. (2007). "Osteonecrosis of the jaw. A newly emerging site-specific osseous pathology in patients with cancer treated with bisphosphonates. Report of five cases and review of the literature." Eur J Intern Med **18**(5): 417-22.

BACKGROUND: Bisphosphonates are commonly used as standard care in the management of patients with advanced-stage cancer involving bone. There has recently been growing concern that the use of bisphosphonates is associated with osteonecrosis of the jaw (ONJ). METHODS: Between 2001 and 2005, five patients with ONJ associated with pamidronate

and zoledronate therapy were diagnosed at our department. The patients had breast cancer, renal carcinoma, mesothelioma, and multiple myeloma, all involving bone. The literature was reviewed. RESULTS: The duration of bisphosphonate therapy before presentation of ONJ ranged from 21 to 36 months. The lesions were localized to the mandible (n=3) and maxilla (n=2). All of the patients presented with pain and exposed bone; in two of them, symptoms began after tooth extraction. A review of the literature through March 2006 identified more than 250 reported cases of ONJ. CONCLUSIONS: The findings in our patients, combined with the literature review, suggest that: (1) the most common clinical presentation of ONJ is pain and exposed bone of the mandible or maxilla; (2) for patients who develop ONJ, conservative, non-surgical treatment is strongly recommended; (3) clinical dental examination and a panoramic jaw radiograph should be performed before patients begin bisphosphonate therapy; (4) dental treatment and other oral procedures should be completed before initiating bisphosphonate therapy; (5) patients should be informed and instructed on the importance of maintaining good oral hygiene and having regular dental assessment; and (6) the medical community needs to be aware of the association between bisphosphonate usage and ONJ so that unnecessary and harmful surgical procedures can be avoided.

Cawood, R., H. H. Chen, et al. (2009). "Use of tissue-specific microRNA to control pathology of wild-type adenovirus without attenuation of its ability to kill cancer cells." PLoS Pathog **5**(5): e1000440.

Replicating viruses have broad applications in biomedicine, notably in cancer virotherapy and in the design of attenuated vaccines; however, uncontrolled virus replication in vulnerable tissues can give pathology and often restricts the use of potent strains. Increased knowledge of tissue-selective microRNA expression now affords the possibility of engineering replicating viruses that are attenuated at the RNA level in sites of potential pathology, but retain wild-type replication activity at sites not expressing the relevant microRNA. To assess the usefulness of this approach for the DNA virus adenovirus, we have engineered a hepatocyte-safe wild-type adenovirus 5 (Ad5), which normally mediates significant toxicity and is potentially lethal in mice. To do this, we have included binding sites for hepatocyte-selective microRNA mir-122 within the 3' UTR of the E1A transcription cassette. Imaging versions of these viruses, produced by fusing E1A with luciferase, showed that inclusion of mir-122 binding sites caused up to 80-fold decreased hepatic expression of E1A following intravenous delivery to mice. Animals administered a ten-times lethal dose of wild-type Ad5 (5x10(10) viral particles/mouse) showed substantial hepatic genome replication and extensive liver pathology, while inclusion of 4 microRNA binding sites decreased replication 50-fold and virtually abrogated liver toxicity. This modified wild-type virus retained full activity within cancer cells and provided a potent, liver-safe oncolytic virus. In addition to providing many potent new viruses for cancer virotherapy, microRNA control of virus replication should provide a new strategy for designing safe attenuated vaccines applied across a broad range of viral diseases.

Chafe, S., L. Honore, et al. (2000). "An analysis of the impact of pathology review in gynecologic cancer." Int J Radiat Oncol Biol Phys **48**(5): 1433-8.

PURPOSE: To analyze the impact of pathology review in gynecologic malignancies. METHODS AND MATERIALS: For all new gynecologic patients seen between December 2, 1993 and January 4, 1996, we conducted a retrospective chart review to determine if a pathology review by the institute's consultant pathologist changed the diagnosis, and if so whether the change altered patient management. A total of 514 patients were seen, of whom 120 had cervical cancer, 226 had endometrial cancer, 122 had a primary ovarian or peritoneal malignancy, 9 had a vaginal malignancy, 28 had vulvar cancer, and 9 had a miscellaneous gynecologic malignancy. RESULTS: On pathology review the diagnosis changed for 200 of 599 specimens (33%). This altered management for 63 of 514 patients (12%). For patients with cervical cancer, the grade of tumor was the main change in pathologic diagnosis, with occasional change in the presence of lymph vascular invasion. These did not translate into patient management alterations. Eight patients (1.5%) had management alterations. The changes in depth of invasion and vascular invasion altered management for 3 patients. Changes in pap smears resulted in two management alterations, and changes in histologic diagnoses altered management for 3 cases. For endometrial primaries the changes in pathologic diagnosis included grade, depth of invasion, and the presence of cervical involvement. This did alter management in 40 cases (8%). For the ovarian malignancies, the main changes were grade, extent of disease, or histologic classification, some of which (10 patients, 2%) resulted in altered management. One patient with a vaginal lesion had the diagnosis changed, which did alter management. Of the patients diagnosed with vulvar cancer, the pathologic diagnosis changed for 11 patients. This included changes in grade and depth of invasion. This altered management of 2 patients. The remaining

miscellaneous gynecologic malignancies had only two diagnosis changes that altered management. CONCLUSIONS: Pathologic review of gynecologic malignancies is justified as it can alter patient management. In addition, the process facilitates cooperation of the multidisciplinary team and provides a valuable educational forum to enhance patient care.

Chan, N. G., A. Duggal, et al. (2008). "Pathological reporting of colorectal cancer specimens: a retrospective survey in an academic Canadian pathology department." Can J Surg **51**(4): 284-8.

OBJECTIVE: To survey and improve the pathological reporting of colorectal cancer (CRC) specimens in a tertiary care pathology department. METHODS: We identified CRC specimens reported in a 6-month period before and after educational sessions and the introduction of a standardized CRC synoptic reporting protocol. Gross and microscopic descriptions were analyzed according to published guidelines for important staging and prognostic features. We then reexamined these parameters for a further 6-month period 15 months later to ensure that the quality of reporting had been maintained. RESULTS: In total, 108 and 166 cases were analyzed before and after standardization, respectively. Many features were reported appropriately, including tumour size, type and grade, depth of invasion, nodal status and proximal and distal margin status. Several underreported features showed significant improvement after standardization, including serosal involvement (reporting increased from 22% to 84%), distance to radial margin (from 14% to 64%), extramural venous invasion (from 18% to 88%), host response (from 19% to 94%) and mean number of nodes retrieved (mean numbers retrieved increased from 11 to 16). The subsequent review 15 months later showed continued long-term improvement in these areas. CONCLUSION: Education and synoptic reporting significantly improved CRC reporting at our centre.

Chun, F. K., T. Steuber, et al. (2006). "Development and internal validation of a nomogram predicting the probability of prostate cancer Gleason sum upgrading between biopsy and radical prostatectomy pathology." Eur Urol **49**(5): 820-6.

OBJECTIVE: Previous reports indicate that as many as 43% of men with low grade PCa at biopsy will be diagnosed with high-grade PCa at RP. We explored the rate of upgrading from biopsy to RP specimen in our contemporary cohort, and developed a model capable of predicting the probability of biopsy Gleason sum upgrading. MATERIALS AND METHODS: The study cohort consisted of 2982 men treated with RP, with available clinical stage, serum prostate specific antigen and biopsy Gleason scores. These clinical data were used as predictors in multivariate logistic regression models (LRM) addressing the rate of Gleason sum upgrading between biopsy and RP pathology. LRM regression coefficients were used to develop a nomogram predicting the probability of Gleason sum upgrading and was subjected to 200 bootstrap resamples for internal validation and to reduce overfit bias. RESULTS: Overall, 875 patients were upgraded (29.3%). In multivariate LRMs, all predictors were highly significant (all p values <0.0001). Bootstrap-corrected predictive accuracy of the nomogram predicting the probability of Gleason sum upgrading between biopsy and RP was 0.804. CONCLUSION: We developed a highly accurate clinical aid for treatment decision-making. It may prove useful when the possibility of a more aggressive Gleason variant may change the treatment options.

Cohen, I., E. Perel, et al. (1999). "Endometrial pathology in postmenopausal tamoxifen treatment: comparison between gynaecologically symptomatic and asymptomatic breast cancer patients." J Clin Pathol **52**(4): 278-82.

AIMS: To evaluate whether endometrial pathology is more likely to be diagnosed in gynaecologically symptomatic rather than in gynaecologically asymptomatic postmenopausal breast cancer patients with tamoxifen treatment; and to evaluate the possible influence of various clinical factors on the incidence of endometrial pathology. METHODS: Endometrial histological findings, transvaginal ultrasonographic endometrial thickness, demographic characteristics, health habits, and risk factors for endometrial cancer were compared between 14 gynaecologically symptomatic (group I) and 224 gynaecologically asymptomatic (group II) postmenopausal breast cancer patients with tamoxifen treatment. RESULTS: Overall, 28.6% of the study population had endometrial pathology. The incidence of overall positive endometrial histological findings was significantly higher in group I than in group II (92.9% v 24.6%, $p < 0.0001$). Atrophic endometrium was more common in group II than in group I (75.3% v 7.1%, $p < 0.0001$). Most other endometrial pathology was significantly more common in group I than in group II (endometrial hyperplasia, 35.7% v 5.6%, $p < 0.0001$; endometrial polyps, 35.7% v 13.4%, $p < 0.0111$; endometrial carcinoma, 21.5% v 0.9%, $p < 0.0001$). Endometrial pathology appeared considerably later in the gynaecologically asymptomatic patients than in gynaecologically symptomatic patients ($p = 0.0002$). Vaginal bleeding or spotting occurred exclusively in group I. The incidence of endometrial pathology in the entire study

population was consistent with that reported elsewhere, and higher than that reported for healthy postmenopausal women. CONCLUSIONS: Endometrial pathology is more likely to be diagnosed in gynaecologically symptomatic postmenopausal breast cancer patients with tamoxifen treatment, and after a shorter duration of time, than in gynaecologically asymptomatic patients.

Compton, C. C. (1999). "Pathology report in colon cancer: what is prognostically important?" Dig Dis **17**(2): 67-79.

Surgical resection is the primary treatment modality for colorectal cancer, and the most powerful tool for assessing prognosis following surgery is pathologic analysis of the resection specimen. Although the parameters that determine the pathologic stage are the strongest predictors of postoperative outcome, a number of additional pathologic features have prognostic significance that is independent of stage. These include: histologic grade; small vessel (lymphatic or venular) invasion; extramural venous invasion; perineural invasion; tumor border configuration; host lymphoid response to tumor, and the status of surgical margins. For specimens in which the radial (circumferential) margin is applicable, surgical clearance around the tumor is also of import. It is self-evident that, compared to data derived from additional assays, prognostic information that can be derived directly from standard histologic sections of a tumor is of the greatest cost-benefit to the patient. In the current era of cost containment, it is essential that surgical pathologists evaluate and report the pathologic features that are of prognostic and/or predictive significance in every case of colorectal cancer and, in turn, that the import of these be understood by the treating physicians.

Cordon-Cardo, C., A. Kotsianti, et al. (2007). "Improved prediction of prostate cancer recurrence through systems pathology." J Clin Invest **117**(7): 1876-83.

We have developed an integrated, multidisciplinary methodology, termed systems pathology, to generate highly accurate predictive tools for complex diseases, using prostate cancer for the prototype. To predict the recurrence of prostate cancer following radical prostatectomy, defined by rising serum prostate-specific antigen (PSA), we used machine learning to develop a model based on clinicopathologic variables, histologic tumor characteristics, and cell type-specific quantification of biomarkers. The initial study was based on a cohort of 323 patients and identified that high levels of the androgen receptor, as detected by immunohistochemistry, were associated with a reduced time to PSA recurrence. The model predicted recurrence with high accuracy, as indicated by a concordance index in the validation set of 0.82, sensitivity of 96%, and specificity of 72%. We extended this approach, employing quantitative multiplex immunofluorescence, on an expanded cohort of 682 patients. The model again predicted PSA recurrence with high accuracy, concordance index being 0.77, sensitivity of 77% and specificity of 72%. The androgen receptor was selected, along with 5 clinicopathologic features (seminal vesicle invasion, biopsy Gleason score, extracapsular extension, preoperative PSA, and dominant prostatectomy Gleason grade) as well as 2 histologic features (texture of epithelial nuclei and cytoplasm in tumor only regions). This robust platform has broad applications in patient diagnosis, treatment management, and prognostication.

Couto, J. P., H. Prazeres, et al. (2009). "How molecular pathology is changing and will change the therapeutics of patients with follicular cell-derived thyroid cancer." J Clin Pathol **62**(5): 414-21.

Well-differentiated thyroid carcinomas comprise two well-defined histological types: papillary and follicular (PTCs and FTCs, respectively). Despite being derived from the same cell (thyroid follicular cell), these two types of tumour accumulate distinct genetic abnormalities during progression. The molecular pathology of thyroid cancer is now better understood because of our ability to identify RET/PTC rearrangements and BRAF mutations in the aetiopathogenesis of the large majority of PTCs and the high prevalence of RAS mutations and PAX8/PPARgamma rearrangements in follicular patterned carcinomas (FTCs and follicular variant of PTCs). This review summarises most of the molecular alterations currently used as targets for new biological treatments and looks at some of the changes that are already occurring or may occur in the treatment of patients with thyroid cancer. For simplicity, the review is divided up according to the major genetic alterations identified in well-differentiated thyroid carcinomas (RET/PTC rearrangements, BRAF mutations, RAS mutations and mitochondrial DNA deletions and mutations) and their respective treatments.

Cserni, G., I. Amendoeira, et al. (2004). "Discrepancies in current practice of pathological evaluation of sentinel lymph nodes in breast cancer. Results of a questionnaire based survey by the European Working Group for Breast Screening Pathology." J Clin Pathol **57**(7): 695-701.

AIMS: To evaluate aspects of the current practice of sentinel lymph node (SLN) pathology in

breast cancer via a questionnaire based survey, to recognise major issues that the European guidelines for mammography screening should address in the next revision. METHODS: A questionnaire was circulated by mail or electronically by the authors in their respective countries. Replies from pathology units dealing with SLN specimens were evaluated further. RESULTS: Of the 382 respondents, 240 European pathology units were dealing with SLN specimens. Sixty per cent of these units carried out intraoperative assessment, most commonly consisting of frozen sections. Most units slice larger SLNs into pieces and only 12% assess these slices on a single haematoxylin and eosin (HE) stained slide. Seventy one per cent of the units routinely use immunohistochemistry in all cases negative by HE. The terms micrometastasis, submicrometastasis, and isolated tumour cells (ITCs) are used in 93%, 22%, and 71% of units, respectively, but have a rather heterogeneous interpretation. Molecular SLN staging was reported by only 10 units (4%). Most institutions have their own guidelines for SLN processing, but some countries also have well recognised national guidelines. CONCLUSIONS: Pathological examination of SLNs throughout Europe varies considerably and is not standardised. The European guidelines should focus on standardising examination. They should recommend techniques that identify metastases > 2 mm as a minimum standard. Uniform reporting of additional findings may also be important, because micrometastases and ITCs may in the future be shown to have clinical relevance.

D'Avolio, L. W., M. S. Litwin, et al. (2007). "Automatic identification and classification of surgical margin status from pathology reports following prostate cancer surgery." AMIA Annu Symp Proc: 160-4.

Prostate cancer removal surgeries result in tumor found at the surgical margin, otherwise known as a positive surgical margin, have a significantly higher chance of biochemical recurrence and clinical progression. To support clinical outcomes assessment a system was designed to automatically identify, extract, and classify key phrases from pathology reports describing this outcome. Heuristics and boundary detection were used to extract phrases. Phrases were then classified using support vector machines into one of three classes: 'positive (involved) margins,' 'negative (uninvolved) margins,' and 'not-applicable or definitive.' A total of 851 key phrases were extracted from a sample of 782 reports produced between 1996 and 2006 from two major hospitals. Despite differences in reporting style, at least 1 sentence containing a diagnosis was extracted from 780 of the 782 reports (99.74%). Of the 851 sentences extracted, 97.3% contained diagnoses. Overall accuracy of automated classification of extracted sentences into the three categories was 97.18%.

Dietel, M. (2007). "Predictive pathology of cytostatic drug resistance and new anti-cancer targets." Recent Results Cancer Res **176**: 25-32.

Due to continuous technical developments and new insights into the high complexity of many diseases, in particular the pathogenesis of cancer, molecular pathology is a rapidly growing field gaining centre stage in the clinical management of tumours as well as in the pharmaceutical development of new anti-cancer drugs. Activated signalling components are the targets for classical therapeutic agents and newly developed inhibitors. The application of the compounds in clinical trials has revealed promising results; however, the current diagnostic procedures available for determining which patients will primarily benefit from rational tumour therapy are insufficient. To read a patients' tissue as "deeply" as possible, gaining information on the morphology and on genetic, proteomic and epigenetic alterations will . be the new task of surgical pathologists experienced in molecular diagnostics, in order to provide the clinicians with information relevant for an individualized medicine. Among the different high-throughput technologies, DNA microarrays are now the first array approaches close to entering routine diagnostics. Technically advanced and well-established microarray platforms can now be evaluated by distinct bioinformatic tools capable of both identifying novel genes associated with disease development and also clusters of genes predicting the clinical outcome of an individual tumour. DNA microarrays have been efficiently used for the classification of tumour subtypes, the prediction of metastatic potential and drug response. In the current review we will focus in particular on the new possibilities of predicting the efficacy of anti-neoplastic drugs as a diagnostic tool of pathologists seeking an efficient individualized therapy.

Dillon, P. W., T. V. Whalen, et al. (1995). "Neonatal soft tissue sarcomas: the influence of pathology on treatment and survival. Children's Cancer Group Surgical Committee." J Pediatr Surg **30**(7): 1038-41.

INTRODUCTION: A multi-institutional study was conducted by the Children's Cancer Group (CCG) to evaluate all soft tissue sarcomas diagnosed within the first month of life. METHODS: A retrospective study by 11 CCG institutions of patient records from 1971 to 1991 were reviewed for demographic data, pathology, therapy, and outcome. RESULTS: 32 neonates with soft tissue sarcomas were identified. There were 21 boys and 11 girls.

Pathology was equally divided into three groups: Congenital fibrosarcoma (CFS) (12), rhabdomyosarcoma (RMS) (11), and non-RMS soft tissue sarcomas (NRSTS) (9). Anatomic sites consisted of head/neck (11), extremity (9), trunk (8), pelvis (3), and unknown (2). Overall survival rate was 59% (19/32). CONCLUSION: Soft tissue sarcomas in the neonate comprise three general groups with survival rates dependent on pathology and extent of disease.

Dome, B., M. J. Hendrix, et al. (2007). "Alternative vascularization mechanisms in cancer: Pathology and therapeutic implications." Am J Pathol **170**(1): 1-15.

Although cancer cells are not generally controlled by normal regulatory mechanisms, tumor growth is highly dependent on the supply of oxygen, nutrients, and host-derived regulators. It is now established that tumor vasculature is not necessarily derived from endothelial cell sprouting; instead, cancer tissue can acquire its vasculature by co-option of pre-existing vessels, intussusceptive microvascular growth, postnatal vasculogenesis, glomeruloid angiogenesis, or vasculogenic mimicry. The best-known molecular pathway driving tumor vascularization is the hypoxia-adaptation mechanism. However, a broad and diverse spectrum of genetic aberrations is associated with the development of the "angiogenic phenotype." Based on this knowledge, novel forms of antivascular modalities have been developed in the past decade. When applying these targeted therapies, the stage of tumor progression, the type of vascularization of the given cancer tissue, and the molecular machinery behind the vascularization process all need to be considered. A further challenge is finding the most appropriate combinations of antivascular therapies and standard radio- and chemotherapies. This review intends to integrate our recent knowledge in this field into a rational strategy that could be the basis for developing effective clinical modalities using antivascular therapy for cancer.

Donovan, M. J., S. Hamann, et al. (2008). "Systems pathology approach for the prediction of prostate cancer progression after radical prostatectomy." J Clin Oncol **26**(24): 3923-9.

PURPOSE: For patients with prostate cancer treated by radical prostatectomy, no current personalized tools predict clinical failure (CF; metastasis and/or androgen-independent disease). We developed such a tool through integration of clinicopathologic data with image analysis and quantitative immunofluorescence of prostate cancer tissue. PATIENTS AND METHODS: A prospectively designed algorithm was applied retrospectively to a cohort of 758 patients with clinically localized or locally advanced prostate cancer. A model predicting distant metastasis and/or androgen-independent recurrence was derived from features selected through supervised multivariate learning. Performance of the model was estimated using the concordance index (CI). RESULTS: We developed a predictive model using a training set of 373 patients with 33 CF events. The model includes androgen receptor (AR) levels, dominant prostatectomy Gleason grade, lymph node involvement, and three quantitative characteristics from hematoxylin and eosin staining of prostate tissue. The model had a CI of 0.92, sensitivity of 90%, and specificity of 91% for predicting CF within 5 years after prostatectomy. Model validation on an independent cohort of 385 patients with 29 CF events yielded a CI of 0.84, sensitivity of 84%, and specificity of 85%. High levels of AR predicted shorter time to castrate prostate-specific antigen increase after androgen deprivation therapy (ADT). CONCLUSION: The integration of clinicopathologic variables with imaging and biomarker data (systems pathology) resulted in a highly accurate tool for predicting CF within 5 years after prostatectomy. The data support a role for AR signaling in clinical progression and duration of response to ADT.

Donovan, M. J., A. Kotsianti, et al. (2009). "A systems pathology model for predicting overall survival in patients with refractory, advanced non-small-cell lung cancer treated with gefitinib." Eur J Cancer **45**(8): 1518-26.

PURPOSE: To identify clinical and biometric features associated with overall survival of patients with advanced refractory non-small-cell lung cancer (NSCLC) treated with gefitinib. EXPERIMENTAL DESIGN: One hundred and nine diagnostic NSCLC samples were analysed for EGFR mutation status, EGFR immunohistochemistry, histologic morphometry and quantitative immunofluorescence of 15 markers. Support vector regression modelling using the concordance index was employed to predict overall survival. RESULTS: Tumours from 4 of 87 patients (5%) contained EGFR tyrosine kinase domain mutations. A multivariate model identified ECOG performance status, and tumour morphometry, along with cyclin D1, caspase-3 activated, and phosphorylated KDR to be associated with overall survival, concordance index of 0.74 (hazard ratio (HR) 5.26, p-value 0.0002). CONCLUSIONS: System-based models can be used to identify a set of baseline features that are associated with reduced overall survival in patients with NSCLC treated with gefitinib. This is a preliminary study, and further analyses are required to validate the model in a randomised, controlled treatment setting.

Faratian, D., S. P. Langdon, et al. (2009). "How can systems pathology help us personalize cancer therapy?" Discov Med **8**(41): 81-6.

Cancer is a complex and heterogeneous disease which changes over time, and in the face of therapeutic intervention. Single tissue biomarkers, while partially successful in helping us understand which patients will respond to therapy, cannot hope to capture this amazing complexity. Systems pathology, which combines measurements made on tissues with new mathematical modeling approaches, permits the testing of new agents and biomarkers in silico through computational analysis. These approaches help us to refine pathological measurements and improve decision making about therapies for clinical trial planning and ultimately personalized therapy.

Ferlito, A. and A. Rinaldo (2000). "The pathology and management of subglottic cancer." Eur Arch Otorhinolaryngol **257**(3): 168-73.

Because there is still considerable controversy concerning the anatomical boundaries separating the three regions of the larynx, cancer of the subglottis remains difficult to manage. We have reviewed the numerous differences in the anatomical definitions used in the literature and the consequent differences in reported findings on the incidence of subglottic cancer and its classification. We have also summarized the pathology of subglottic malignant neoplastic lesions, their presenting symptoms and tendency for spread, and the use of imaging methods in its diagnosis. Suitable forms of treatment are discussed, as are considerations on prognosis.

Fortner, J. G., G. Y. Lauwers, et al. (1994). "Nativity, complications, and pathology are determinants of surgical results for gastric cancer." Cancer **73**(1): 8-14.

BACKGROUND: About half the patients involved in the current study were born outside of the United States. Epidemiologic and histologic features and survival estimates were compared with persons born in the United States. Results of gastrectomy with lymph node dissection were studied. METHODS: Records of 187 patients with adenocarcinoma of the stomach were reviewed. Seventy-six with a curative gastrectomy were staged retrospectively. Univariate and multivariate analyses were done. RESULTS: Seventy-six percent of histologically reviewed curative resections had the intestinal subtype with the same frequency in U.S.-born and foreign-born patients. Fewer patients with proximal third lesions were foreign born. Thirty-six percent had complications. The overall 5-year Kaplan-Meier survival estimate was 46%: 77% for patients with negative nodes and 33% for patients with positive nodes. N1 survival estimate was 44%; N2, 25%; N3(M1), 0%. All six patients with early gastric cancer are alive 50-147 months after surgery. Other stage I patients had estimated survival of 65%; Stage II, 52%; Stage III, 40%; and Stage IV, 0%. Multivariate analysis revealed four significant prognostic variables: nativity, histologic subgroup, presence of complications, and number of positive nodes. CONCLUSIONS: Proximal gastric cancer was more common in U.S.-born persons. Gastric cancer may be more malignant in U.S.-born persons than in foreign-born persons because their survival was significantly poorer. Complications, a significant adverse factor, were more common in U.S. series. Pancreatectomy with gastrectomy is rarely indicated, because microscopic involvement is rare and complications frequent. The prognostic advantage of a regional lymphadenectomy remains unclear.

Fotiou, S., A. Tserkezoglou, et al. (1998). "Tamoxifen associated uterine pathology in breast cancer patients with abnormal bleeding." Anticancer Res **18**(1B): 625-9.

The purpose of this study was to evaluate the underlying pathology in breast cancer patients treated with tamoxifen who present with abnormal bleeding. A total of 56 cases were studied and the histopathologic features of 50 curettage and 18 laparotomy specimens were reviewed. All patients were under tamoxifen treatment (10-40 mg daily) for a period ranging from 5 months to 15 years. Cervical and endometrial polyps were the most common finding in the D and C material (44%). Hyperplasia was the most frequent feature identified at hysterectomy, often combined with leiomyomas, adenomyosis and ovarian tumors. Five primary adenocarcinomas of the endometrium, most of them Stage I beta, Grade I minimally invading, were found as well. These data support the hypothesis that tamoxifen exerts a proliferative estrogen-like effect on the uterus. Abnormal bleeding in women under TAM treatment warrants prompt investigation and careful follow up of the patients.

Francis, J. A., M. M. Weir, et al. (2009). "Should preoperative pathology be used to select patients for surgical staging in endometrial cancer?" Int J Gynecol Cancer **19**(3): 380-4.

INTRODUCTION: The decision to offer surgical staging in endometrial cancer is often based on preoperative histology and grade from endometrial biopsy or dilatation and curettage. The primary objective of this study was to evaluate the concordance between preoperative and final pathology from a population-based study of endometrial cancer to address whether preoperative biopsy is a reliable

determinant in selecting patients for surgical staging. METHODS: Retrospective cohort study in Ontario, Canada, from 1996 to 2000. The study included all women with a preoperative diagnosis of endometrioid adenocarcinoma on endometrial biopsy or dilatation and curettage, followed by definitive surgery. All other histological types were excluded. Surgical staging rates were compared according to preoperative pathology. Primary outcome measure was the concordance between preoperative and final pathology, expressed as a Spearman correlation coefficient (rho). A multivariable logistic regression estimated the effects of demographic variables and grade on our outcome measure. RESULTS: There were 1804 evaluable cases in this study. For preoperative grades 1, 2, and 3 endometrioid adenocarcinoma, surgical staging rates were 9.1%, 13.7%, and 25.6%, respectively. Concordance rates with final pathology were 73%, 52%, and 53%, respectively. There was only moderate concordance between preoperative and final pathology (rho = 0.52). There was no significant difference in concordance rates according to age, year, or hospital volume, but lower concordance rates among teaching hospitals. CONCLUSION: Preoperative biopsy has only a moderate ability to predict final pathology in endometrial cancer, and therefore, additional factors should be considered in selecting patients for a surgical staging procedure.

Franklin, W. A. (2000). "Diagnosis of lung cancer: pathology of invasive and preinvasive neoplasia." Chest **117**(4 Suppl 1): 80S-89S.

The histopathologic appearance of lung carcinoma remains an important guide to prognosis and treatment. The newly revised World Health Organization classification retains the broadest pathologic categories of the older classification but includes several revisions, including the elimination of the small cell, intermediate cell type category; the addition of large cell neuroendocrine and spindle/giant cell categories; and an extended consideration of preneoplastic lesions. The histopathologic classification of lung cancer is expected to continue to change as clinical practice and biological understanding of these tumors change. The application of immunohistochemical testing to histologic material not only provides new assistance with conventional histologic classification, but also permits new ways to subclassify tumors, the full clinical significance of which is yet to be realized. The significance of expression of neuroendocrine markers, histologic grading of response to chemotherapy, and delineation of morphologic changes preceding the occurrence of invasive carcinoma are all areas where understanding microscopic cellular changes in the airways will be critical for clinical advance.

Franklin, W. A. (2000). "Pathology of lung cancer." J Thorac Imaging **15**(1): 3-12.

Microscopic examination of stained smears and tissue sections remains the standard method for definitive diagnosis and classification of lung cancer. However, the morphology of lung cancer is complex, and consensus classifications such as those prepared by a panel World Health Organization (WHO) are required for the sake of consistency and clinical relevance. In the most recent (1999) WHO classification, the diagnostic categories of greatest clinical importance, small cell lung carcinoma and non-small cell lung carcinoma, remain fundamentally unchanged. However, application of immunohistochemistry and electron microscopy has revealed expression of neuroendocrine markers in a wide variety of tumors. Expression of these markers is not taken into account in current treatment protocols, and additional correlative studies will be required to determine the clinical relevance of neuroendocrine differentiation in lung carcinoma. In addition to histological classification, microscopic analysis can provide in situ evidence of response to chemotherapy, as well as information on precursor lesions and multistep carcinogenesis in the airways. Finally, it is likely that morphological assessment of lung carcinoma and preneoplastic lesions will continue to be refined as new diagnostic modalities such as spiral computed tomography and fluorescence bronchoscopy provide previously inaccessible specimens for morphological and correlative molecular studies.

Freedland, S. J., G. S. Csathy, et al. (2002). "Percent prostate needle biopsy tissue with cancer is more predictive of biochemical failure or adverse pathology after radical prostatectomy than prostate specific antigen or Gleason score." J Urol **167**(2 Pt 1): 516-20.

PURPOSE: Biopsy Gleason score, serum prostate specific antigen (PSA) levels, and clinical stage are known to be independent predictors of adverse pathological features and biochemical failure after radical prostatectomy. We determine whether various prostate needle biopsy parameters were predictive of either adverse pathological findings or disease recurrence after radical prostatectomy. MATERIALS AND METHODS: A single pathologist reviewed the prostate needle biopsy specimens of 190 men who underwent radical prostatectomy between 1991 and 2000. Biopsy specimens were examined for Gleason score, perineural invasion, number and percent of cores with cancer, and percent of total biopsy tissue with cancer and Gleason grade 4 or 5 cancer. Multivariate analysis was used to determine

the prostate needle biopsy parameters and preoperative clinical variables, including serum PSA, clinical stage, patient age and race, that were most significant for predicting positive surgical margins, nonorgan confined disease, seminal vesicle invasion and biochemical failure after radical prostatectomy. RESULTS: Of the prostate needle biopsy parameters examined percent of tissue with cancer was the strongest predictor of biochemical recurrence in the multivariate analysis ($p < 0.001$). Percent of tissue with cancer was a stronger predictor of biochemical recurrence than either PSA ($p = 0.048$) or biopsy Gleason score ($p = 0.053$). It was also a strong independent predictor of seminal vesicle invasion ($p = 0.015$) and nonorgan confined disease ($p = 0.024$). Perineural invasion, percent and number of cores with cancer, and percent of tissue with Gleason grade 4 or 5 were not independent predictors of either adverse pathology or biochemical failure. CONCLUSIONS: Of all the preoperative variables examined, including the standard clinical variables of serum PSA, Gleason score and clinical stage, percent of biopsy tissue with cancer was the strongest predictor of biochemical recurrence, seminal vesicle invasion and nonorgan confined disease. Consideration should be given to reporting percent of total biopsy tissue with cancer in all prostate biopsy results.

Furukawa, T. and A. Horii (2004). "Molecular pathology of pancreatic cancer: in quest of tumor suppressor genes." Pancreas **28**(3): 253-6.

To find molecular clues useful for early detection and effective therapy for pancreatic cancer, we first carried out genomic analysis by means of comparative genomic hybridization and micro-satellite analysis. We found very complicated molecular alterations in multiple chromosomal regions, including 1p, 6q, 9p, 12q, 17p, 18q, and 21q for losses and 8q and 20q for gains. These diverse changes are very characteristic of pancreatic cancer, and from this information, we developed a method for detecting the aberrant copy numbers of specific chromosomal regions by fluorescence in situ hybridization in cells collected from pancreatic juice for early diagnosis of pancreatic neoplasms. The regions of losses suggest the existence of tumor suppressor genes (TSGs). We identified DUSP6/MKP-3 at 12q21-q22 as a strong candidate TSG; it showed epigenetic inactivation in some fractions of invasive pancreatic cancer and growth suppression and apoptosis by overexpression in vitro. To determine the pathologic roles of 18q, we introduced a normal copy of chromosome 18 into cultured pancreatic cancer cells. The introduction induced marked suppressions of tumor formation and metastasis formation in vivo. We continue work to more completely understand the complex molecular mechanisms of pancreatic carcinogenesis and to apply the information gained to the clinical treatment of pancreatic cancer.

Gathani, T., J. Green, et al. (2008). "Pathology reports provided reliable and readily accessible records of surgical procedures performed in women with breast cancer." J Clin Epidemiol **61**(4): 402-6.

OBJECTIVE: Extracting complete and accurate records of surgical procedures from case-notes is time consuming and laborious. We compared the completeness and time taken to extract data on surgical procedures from case-notes and from pathology reports. STUDY DESIGN AND SETTING: Information on surgical procedures was extracted from pathology reports and hospital case-notes for 111 women with breast cancer in three centers. The time taken to perform this task was recorded. Surgical procedures were classified into diagnostic and therapeutic procedures, and analysis was performed to determine the completeness and accuracy of the documentation of the procedures. RESULTS: The average time taken to extract relevant information from the pathology reports (3.0 minutes) was one-fifth that for the case-notes (14.4 minutes). The case-notes documented slightly fewer procedures than the pathology records: 94 vs. 108 diagnostic and 108 vs. 110 therapeutic procedures, respectively. Of the 219 therapeutic and diagnostic surgical procedures recorded by both data sources, for 216 procedures there was exact agreement as to the specific type of procedure performed. CONCLUSIONS: Extraction of information on surgical procedures is faster from pathology records than from case-notes. The level of agreement for the specific type of procedure performed is excellent and, if anything, the pathology records are more complete than the case-notes.

Gerber, B., A. Krause, et al. (2006). "Anastrozole versus tamoxifen treatment in postmenopausal women with endocrine-responsive breast cancer and tamoxifen-induced endometrial pathology." Clin Cancer Res **12**(4): 1245-50.

PURPOSE: To investigate the effect of switching from adjuvant tamoxifen to anastrozole (Arimidex) treatment in postmenopausal women with endocrine-responsive breast cancer and histologically proven tamoxifen-induced benign endometrial pathology. EXPERIMENTAL DESIGN: Two hundred twenty-six postmenopausal women who had received adjuvant tamoxifen 20 mg/d (> or =12 months, < or =48 months) and developed abnormal vaginal bleeding and/or an asymptomatic endometrial thickness >10 mm [measured by transvaginal ultrasound (TVUS)] were subjected to hysteroscopy and dilation and curettage (D&C). Thereafter, 171

patients were randomized in a phase III study to continue tamoxifen treatment (n = 88) or switch to anastrozole 1 mg/d (n = 83). Patients were monitored for < or =42 months using TVUS at 6-monthly intervals. RESULTS: At study entry, there were no significant differences in vaginal bleeding, endometrial thickness, and histologic findings between the two treatment groups. Throughout the treatment period, there was no significant difference in recurrent vaginal bleeding between groups [anastrozole, 4 of 83 (4.8%); tamoxifen, 9 of 88 (10.2%); P = 0.18]. Six months after randomization, the mean endometrial thickness for patients who switched to anastrozole was significantly reduced compared with those who continued tamoxifen treatment (P < 0.0001). Significantly fewer anastrozole patients required a repeat hysteroscopy and D&C compared with those on tamoxifen [4 of 83 (4.8%) and 29 of 88 (33.0%), respectively; P < 0.0001]. Repeat hysteroscopy and D&C revealed endometrial atrophy in all 4 cases in the anastrozole group and 14 polyps, 8 hyperplasias, and 7 atrophies in the tamoxifen group. CONCLUSIONS: Switching from tamoxifen to anastrozole treatment significantly reduced the need for a second hysteroscopy and D&C due to recurrent vaginal bleeding or thickening of the endometrium in postmenopausal breast cancer patients with tamoxifen-induced endometrial abnormalities.

Gibson, L. E., R. R. Barakat, et al. (1996). "Endometrial pathology at dilatation and curettage in breast cancer patients: comparison of tamoxifen users and nonusers." Cancer J Sci Am **2**(1): 35-8.

PURPOSE: We conducted this retrospective study to determine the endometrial pathologic findings at the time of dilatation and curettage in breast cancer patients on tamoxifen and compare these findings with those from a similar group of patients not receiving tamoxifen. METHODS: The pathologic findings from endometrial curettings in all breast cancer patients who underwent a dilatation and curettage between January 1986 and June 1993 at our institution were retrospectively reviewed. Medical records and office charts were reviewed to determine the patient age, history, and duration of tamoxifen use, and the presence of symptoms (vaginal spotting or bleeding). RESULTS: Two hundred and forty breast cancer patients were identified. Seventy-five patients (31%) were taking tamoxifen (mean duration, 26 months) at the time of dilatation and curettage. Fifty-three of these patients were symptomatic. Twenty-two of the patients taking tamoxifen were asymptomatic. One hundred and sixty-five patients (69%) were not taking tamoxifen. Of these patients, 109 were symptomatic and 56 were asymptomatic. In both symptomatic and asymptomatic breast cancer patients, there was no difference in the incidence of endometrial polyps, hyperplasia, or adenocarcinoma when comparing tamoxifen users with nonusers. CONCLUSION: Short-term tamoxifen use in breast cancer patients was not found to alter the endometrial pathologic findings at the time of dilatation and curettage.

Guarino, M., B. Rubino, et al. (2007). "The role of epithelial-mesenchymal transition in cancer pathology." Pathology **39**(3): 305-18.

Invasion, the hallmark of malignancy, consists in the translocation of tumour cells from the initial neoplastic focus into neighbouring host tissues, and also allows tumour cells to penetrate vessel endothelium and enter the circulation to form distant metastasis. A histological pattern found at the periphery of carcinomas is the presence of individual malignant cells detached from the tumour mass and staying independently within the interstitial matrix of the stroma. While they are readily identified by the pathologist as invading malignant cells, their relationship with the compact-appearing portions of the tumour as well as the mechanism underlying the development of this pattern are not immediately evident at histological level. There is growing evidence suggesting that this change in tumour tissue architecture takes place through a peculiar phenotype modulation known as epithelial-mesenchymal transition (EMT). The essential features of EMT are the disruption of intercellular contacts and the enhancement of cell motility, thereby leading to the release of cells from the parent epithelial tissue. The resulting mesenchymal-like phenotype is suitable for migration and, thus, for tumour invasion and dissemination, allowing metastatic progression to proceed. Although the molecular bases of EMT have not been completely elucidated, several interconnected transduction pathways and a number of signalling molecules potentially involved have been identified. These include growth factors, receptor tyrosine kinases, Ras and other small GTPases, Src, beta-catenin and integrins. Most of these pathways converge on the down-regulation of the epithelial molecule E-cadherin, an event critical in tumour invasion and a 'master' programmer of EMT. E-cadherin gene is somatically inactivated in many diffuse-type cancers such as lobular carcinoma of the breast and diffuse gastric carcinoma, in which neoplastic cells through the entire tumour mass have lost many of their epithelial characteristics and exhibit a highly invasive, EMT-derived histological pattern. E-cadherin down-modulation is also seen in solid, non-diffuse-type cancers at the tumour-stroma boundary where singly invading, EMT-derived tumour cells are seen in histological sections. In this latter scenario, E-cadherin loss and EMT could be

transient, reversible processes possibly regulated by the tumour microenvironment and, as a matter of fact, neoplastic cells that have undergone EMT during invasion seem to regain E-cadherin expression and their epithelial, cohesive characteristics at the secondary foci. Since the molecules involved in EMT represent potential targets for pharmacological agents, these findings open new avenues for the control of metastatic spread in the treatment of malignancies.

Guldner, L., N. Haddy, et al. (2006). "Radiation dose and long term risk of cardiac pathology following radiotherapy and anthracyclin for a childhood cancer." Radiother Oncol **81**(1): 47-56.

PURPOSE: To determine the cardiac status in children 15 years (yrs) or more after a solid tumour treatment. PATIENTS AND METHODS: Of the 447 patients, 229 were fully studied and 218 were not. The following cardiac evaluation was proposed to all the 447 consecutive patients: (1) cardiac Doppler US by one of two expert cardiologists; (2) cardiac rhythm and conduction abnormalities including 24-h holter ECG; (3) (131)I-mIBG myocardial scintigraphy; (4) serum brain natriuretic peptide levels at rest; (5) an exercise test with VO(2)max measurement. The radiation dose delivered to 7 points in the heart was estimated for all patients who had received radiotherapy. RESULTS: Cardiac disorder was diagnosed in 89 evaluated patients (39%) including 24 heart failures and 65 other asymptomatic cardiac diseases. When adjusting on potential confounders, cardiac disorder and cardiac failure risks were respectively linear (ERR at 1 Gy: 26%) and linear-quadratic (ERR at 1 Gy: 19%) functions of the average radiation dose received to the heart. No interaction between cumulative dose of adriamycin and average radiation dose was evidenced for cardiac disorders, but the ERR/Gy of cardiac failure was higher for patients receiving less than 350 mg/m(2) of Adriamycin. CONCLUSION: Long term heart pathologies are probably one of the major iatrogenic risks encored by patients who survived a childhood cancer. This study strongly emphasizes the need to limit the heart irradiation during radiotherapy, particularly, for patients who also received or were susceptible to later received adriamycin.

Hanby, A. M. (2005). "The pathology of breast cancer and the role of the histopathology laboratory." Clin Oncol (R Coll Radiol) **17**(4): 234-9.

Histopathology plays an important part in determining the treatment strategy for women with breast cancer, with the evaluation of breast specimens determining the surgical and the oncological therapeutic options used. The correct approach to specimens requires integration of clinical and imaging findings. This work is not trivial. It is time-consuming and skilled, and requires (and has in place) safeguards and checks in the form of national audit and quality-control schemes. The pathobiology of breast cancer is diverse, and the current taxonomy, rooted in morphological interpretation, has been underscored by molecular observations, such as the relationship of E-cadherin mutations to lobular carcinomas. Investigation of ductal carcinoma of no special type (NST) reveals covert tumour types, such as those with basal or myoepithelial features, whose distinctive features are only now being widely recognised. With the rise of modern molecular techniques, the demise of diagnostic histopathology has been predicted, but, for now and the intermediate future, the histopathologist remains a key element of the integrated breast-care team.

Hannemann, M., J. Weeks, et al. (2008). "Incidence, pathology and outcome of gynaecological cancer in patients under the age of 21 years in South-west England 1995-2004: comparison of data from regional, national and international registries." J Obstet Gynaecol **28**(7): 722-7.

We analysed the incidence, tumour types, management and outcome of gynaecological cancer diagnosed from 1995-2004 in females <21 years in south-west England. Data from the South West Cancer Intelligence Service were compared with those from regional and national registries. A total of 63 patients had gynaecological malignancies: 49 ovarian; nine cervical; the remainder vaginal, uterine or pelvic. The median age was 16 years. Germ cell tumours (26) and carcinomas (6) were the commonest primary ovarian and cervical tumours respectively. Most patients had fertility-sparing procedures. Only seven required re-operation. Information about chemoradiotherapy was incomplete. Four deaths occurred. All patients were followed >3 years and 68% >5 years, with 94% survival to date. Fertility preservation did not impair survival. Mortality is an inadequate indicator of outcome; cancer registries should record information on fertility and pregnancy outcomes, second tumours and long-term treatment-related complications. Improved management requires greater centralised assessment of histology, follow-up and adjuvant treatment.

Harnsberger, J. R., P. Charvat, et al. (1994). "The role of intrarectal ultrasound (IRUS) in staging of rectal cancer and detection of extrarectal pathology." Am Surg **60**(8): 571-6; discussion 576-7.

Intrarectal Ultrasound (IRUS) is rapidly becoming an effective tool in the staging of rectal cancer. Twenty-nine consecutive patients with adenocarcinoma of the rectum underwent both CT

scanning and IRUS in the preoperative assessment of rectal cancer in an effort to correlate IRUS staging with surgical pathology, correlate tumor staging comparing IRUS with CT scan, and determine incidence of extrarectal pathology by IRUS. Patients were reviewed as to IRUS stage, results of CT scan, TNM stage of extirpated tumor, incidence of genitourinary pathology, and sonographic result of preoperative radiotherapy (RT). The mean age of all patients was 69 years; there were 25 males and four females. Twenty-four patients underwent proctectomy with either low pelvic anastomosis or end stoma; five underwent local surgical therapy. Thirteen patients received preoperative RT. CT scan correlated poorly with IRUS staging of tumors penetrating the muscularis propria. IRUS overstaged 40 per cent, understaged 5 per cent, and correctly staged 55 per cent of patients when compared with pathological specimens. Eleven of the 25 males (44 per cent) had abnormal prostates by IRUS. Five (20%) had further urologic intervention, resulting in two prostatic cancers found. Our data suggests that CT scan staging correlated poorly with IRUS staging. CT poorly determines depth of rectal tumor wall invasion. IRUS correlated well with pathology and understaged 5 per cent of patients before surgery. Genitourinary abnormalities were detected in a significant number of patients. IRUS is an effective modality for preoperative staging of rectal cancer.(ABSTRACT TRUNCATED AT 250 WORDS)

Hieken, T. J., J. Harrison, et al. (2001). "Correlating sonography, mammography, and pathology in the assessment of breast cancer size." Am J Surg **182**(4): 351-4.

BACKGROUND: With the increasing use of neoadjuvant and minimally invasive therapy, the accuracy of preoperative determination of breast tumor size becomes important. Therefore, we undertook this study to compare mammography and ultrasonography (US). METHODS: A total of 180 invasive breast cancer patients were prospectively examined by mammography and US; 146 eligible patients had tumors visualized by both modalities. RESULTS: In 69% of cases, US was better than or equivalent to mammography in determining tumor size. Both underestimated tumor size; mean (median) underestimation was 3.8 +/- 0.7 mm (1.7 mm) by US and 3.5 +/- 0.9 mm (2 mm) by mammogram. Maximal tumor dimension was accurate within 5 mm in 65% of cases by mammography and 75% of cases by US. For mammographically determined size (versus pathologic size) correlation, r, was 0.4 and for US it was 0.63 and improved for only T1 and T2 tumors. CONCLUSIONS: These data suggest that US is more accurate than mammography in assessing breast cancer size.

Hirao, Y., S. Ozono, et al. (1994). "Prospective randomized study of prophylaxis of superficial bladder cancer with epirubicin: the role of a central pathology laboratory. Nara Uro-oncology Research Group. (NUORG)." Cancer Chemother Pharmacol **35 Suppl**: S36-40.

The preliminary results of a multi-institutional prospective randomized study of the prophylaxis of superficial bladder cancer using epirubicin (protocol NUORG SBT-003) are reported. The subjects were 129 patients with untreated superficial bladder cancer (< or = T1b, < or = G2) who were randomized into 2 groups: a transurethral resection (TUR)-alone group (63 patients) and a TUR + intravesical epirubicin (20 mg/40 ml, 30 times/2 years) group (66 patients). The nonrecurrence rate observed in the epirubicin group was significantly higher than that seen in the control group. To unify the pathological diagnosis, a central pathology laboratory (CPL) was set up for extramural review. The correspondence of the pathological diagnosis of TUR-Bt specimens between the CPL and the local pathology laboratory (LPL) was 70.5% in grading and 51.9% in staging. There was a tendency for overdiagnosis by the LPL for both the grade and the stage of tumors. However, differing interpretations by pathologists seem to exert little influence on the nonrecurrence rate at interim analysis. Further observation will be necessary to clarify the prophylactic efficacy of low-dose, long-term periodic intravesical epirubicin instillation and the influence of the disagreement in pathological findings between the CPL and the LPL on the analysis of the results.

Honrado, E., J. Benitez, et al. (2004). "The pathology of hereditary breast cancer." Hered Cancer Clin Pract **2**(3): 131-8.

Several studies have demonstrated that familial breast cancers associated with BRCA1 or BRCA2 germline mutations differ in their morphological and immunohistochemical characteristics. Cancers associated with BRCA1 are poorly differentiated infiltrating ductal carcinomas (IDCs) with higher mitotic counts and pleomorphism and less tubule formation than sporadic tumours. In addition, more cases with the morphological features of typical or atypical medullary carcinoma are seen in these patients. Breast carcinomas from BRCA2 mutation carriers tend to be of higher grade than sporadic age-matched controls. Regarding immunophenotypic features. BRCA1 tumours have been found to be more frequently oestrogen receptor-(ER) and progesterone receptor-(PR) negative, and

p53-positive than age-matched controls, whereas these differences are not usually found in BRCA2-associated tumours. A higher frequency and unusual location of p53 mutations have been described in BRCA1/2 carcinomas. Furthermore, BRCA1- and BRCA2-associated breast carcinomas show a low frequency of HER-2 expression. Recent studies have shown that most BRCA1 carcinomas belong to the basal cell phenotype, a subtype of high grade, highly proliferating ER/HER2-negative breast carcinoma characterized by the expression of basal or myoepithelial markers, such as basal keratins, P-cadherin, EGFR, etc. This phenotype occurs with a higher incidence in BRCA1 tumours than in sporadic carcinomas and is rarely found in BRCA2 carcinomas. Hereditary carcinomas not attributable to BRCA1/2 mutations have phenotypic similarities with BRCA2 tumours, but tend to be of lesser grade and lower proliferation index. The pathological features of hereditary breast cancer can drive specific treatment and influence the process of mutation screening.

Honrado, E., J. Benitez, et al. (2005). "The molecular pathology of hereditary breast cancer: genetic testing and therapeutic implications." Mod Pathol **18**(10): 1305-20.

Cancer arising in carriers of mutations in the BRCA1 and BRCA2 genes differs from sporadic breast cancer of age-matched controls and from non-BRCA1/2 familial breast carcinomas in its morphological, immunophenotypic and molecular characteristics. Most BRCA1 carcinomas have the basal cell phenotype, a subtype of high-grade, highly proliferating, estrogen receptor- and HER2-negative breast carcinomas, characterized by the expression of basal or myoepithelial markers such as basal keratins, P-cadherin, epidermal growth factor receptor, etc. This phenotype is rarely found in BRCA2 carcinomas, which are of higher grade than sporadic age-matched controls, but tend to be estrogen receptor- and progesterone receptor-positive. The expression of the cell-cycle proteins cyclins A, B1 and E and SKP2 is associated with a BRCA1 phenotype, whereas cyclin D1 and p27 expression is associated with BRCA2 carcinomas. Recent studies have shown that hereditary carcinomas that are not attributable to BRCA1/2 mutations have phenotypic similarities to BRCA2 tumors, but tend to be of lower grade and proliferation index. Somatic mutations in the BRCA genes are rarely found in hereditary tumors; by contrast, BRCA1 and BRCA2 loss of heterozygosity (LOH) is found in almost all BRCA1 and BRCA2 carcinomas, respectively. Furthermore, all types of hereditary breast carcinomas have a low frequency of HER2 expression. Finally, comparative genomic hybridization studies have revealed differences in chromosomal gains and losses between genotypes. The pathological and molecular features of hereditary breast cancer can drive specific treatments and influence the process of mutation screening. In addition, detecting molecular changes such as BRCA1/2 LOH in nonatypical cells obtained by random fine-needle aspiration, ductal lavage or nipple aspirate fluid may help to earlier identify carrier women who are at an even higher risk of developing breast carcinoma.

Huben, R. P. and J. Gaeta (1996). "Pathology and its importance in evaluating outcome in patients with superficial bladder cancer." Semin Urol Oncol **14**(1 Suppl 1): 23-9.

Subtle cytologic and histologic nuances have a major impact on diagnosis and, consequently, on therapy for superficial bladder cancer. Therefore, the urologist and the pathologist must carefully assess all clinical findings before a course of treatment can be determined. The urologist must advise the pathologist of all the circumstances surrounding a biopsy--whether its purpose is for preliminary clinical impression or diagnosis, the patient's recent treatment history, the availability of previous biopsy specimens for comparison, a thorough history of treatments that may induce characteristic cytologic changes that might lead to misdiagnosis, and alternate diagnostic possibilities drawn from initial pathology and treatment history. Armed with this information, the task of the pathologist is to provide as much data as possible regarding tumor histopathology from the biopsy specimens. Thus, establishment of a close working relationship between the urologist and the pathologist is an important tool for (1) initially characterizing superficial bladder cancer, which is essential in determining an appropriate course of treatment, and (2) accurately evaluating follow-up biopsies to determine the effectiveness of that treatment.

Imperato, P. J., J. Waisman, et al. (2002). "Breast cancer pathology practices among Medicare patients undergoing unilateral extended simple mastectomy." J Womens Health Gend Based Med **11**(6): 537-47.

OBJECTIVE: Information in pathology reports of breast cancer specimens is of critical importance to treating physicians for selection of local regional treatment and adjuvant therapy, evaluation of therapy, estimation of prognosis, and analysis of outcomes. This information is also of great importance to patients and their families. The Cancer Committee of the College of American Pathologists (CAP) and the Association of Directors of Anatomic and Surgical Pathology (ADASP) have published protocols for reporting the findings on breast cancer specimens to

encourage adequate specimen examination and promote the reporting of findings in standardized formats and to provide treating physicians and their patients with vital information. METHODS: To assess the quality of breast cancer pathology practices and the degree to which they agree with published guidelines, we undertook a retrospective analysis among Medicare patients in New York State. Our random sample consisted of 748 (43.5%) of the 1718 cases of unilateral extended simple mastectomy, also referred to as total mastectomy with lymph node dissection (ICD-9-CM procedure code 85.43), for calendar year 1999. Of these, 555 (74.2%) were available for study, whereas the rest did not satisfy inclusion criteria. Among the 555 cases, 545 (98.2%) were women, and 10 (1.8%) were men. The gender distribution was proportionately the same at 98.2% and 1.8% for all 1718 cases. RESULTS: We examined the 555 hospital records for 16 elements (quality indicators). Aggregate performance on 7 of these was > or =83.7%, and performance was < or = 69.4% on 9 others. There were significant interhospital disparities in performance levels for a number of quality indicators. Although some hospitals always recorded certain indicators, others never did. CONCLUSIONS: The issues with breast cancer pathology reports identified in this study are amenable to improvement to better serve patients, especially women, and their treating physicians in making adjuvant decisions, estimating prognosis, and evaluating outcomes.

Imperato, P. J., J. Waisman, et al. (2003). "Improvements in breast cancer pathology practices among medicare patients undergoing unilateral extended simple mastectomy." Am J Med Qual **18**(4): 164-70.

The information contained in pathology reports of breast cancer specimens is of critical importance to treating physicians for selection of local regional treatment, adjuvant therapy, evaluation of therapy, estimation of prognosis, and analysis of outcomes. This information is also of great importance to patients and their families. In 2000, a Breast Cancer Pathology Advisory Group was formed to advise on the design of a project to assess the quality of pathology reports on unilateral extended simple mastectomy (ICD-9-CM procedure code 85.43) specimens from Medicare patients in New York State. This group comprised clinical pathologists, breast surgeons, medical oncologists, clinical breast cancer specialists, and a radiation oncologist. The group suggested that the reports be examined for several elements (quality indicators) that are relevant to patient care and prognosis. Baseline random sample data assessing these elements were established from a random sample of all cases for the calendar year 1999. A random sample of 748 cases (43.5%) of unilateral extended simple mastectomy was chosen from among 1718 cases for the calendar year 1999. Of these, 555 (74.2%) were suitable for review. The remaining 193 (25.8%) cases did not satisfy the inclusion criteria. Aggregate performance on 7 quality indicators (presence of carcinoma, laterality of specimen, number of lymph nodes present, number of positive nodes, documentation of lymph nodes, histologic type, and largest dimension of the tumor) was 83.7% or better, whereas performance was 69.4% or less on 10 others (resection margin status, verification of tumor size, gross observation of the lesion, histologic grade, angiolymphatic invasion, nuclear grade, location of the tumor, mitotic rate, extent of tubule formation, and perineural invasion). The last, perineural invasion, was used as a control element and was not considered an evaluative quality indicator. Performance levels for New York State were significantly lower for histologic grade, resection margin status, and angiolymphatic invasion than in similar studies elsewhere. In addition, there were significant interhospital disparities in the performance levels for these quality indicators. Whereas some hospitals always recorded certain indicators, others never did. This in part reflects differing degrees of adoption of recommended specialty society protocols. The second phase of the project consisted of an educational feedback program involving the directors of pathology laboratories in New York State. The aggregate findings of the baseline study were shared with all the pathologists. In addition, each hospital that performed unilateral extended simple mastectomies during the study period received its own specific data so that it could compare its performance with the aggregate performance. The results of the baseline study also were shared with the New York Pathological Society and the New York State Society of Pathologists. The latter described the results in its newsletter. A postintervention review of the medical charts of a sample of 297 Medicare patients discharged from New York State acute care hospitals with an ICD-9-CM procedure code of 85.43 (unilateral extended simple mastectomy) was conducted for the 6-month period from December 1, 2001, through May 31, 2002. The 8 quality indicators, performance for which was below 84% in the baseline, were chosen for this remeasurement. Statistically significant improvements ($P < .0001$) occurred in all the 8 quality indicators, ranging from 12.6% to 19.9%. The results of this study indicate that the issues identified by breast cancer pathology reports are amenable to improvement. Such improvement can serve both the patients and the treating physicians better in making adjuvant treatment decisions, estimating prognosis, and evaluating outcomes. It also will be of help to

patients and their families in making other life decisions.

Ismaili, N., S. Arifi, et al. (2009). "Small cell cancer of the bladder: pathology, diagnosis, treatment and prognosis." Bull Cancer **96**(6): E30-44.

Small cell carcinoma of the bladder (SCCB) is rare, highly aggressive and diagnosed mainly at advanced stages. In addition, coexistence of SCCB with other types of carcinoma is common. Hematuria is the main symptom of this malignancy. Histological tests show a tumour, which is indistinguishable from small cell lung carcinoma (SCLC). Then immunohistochemistry tests may be helpful for a more precise diagnosis. Pathogenesis is uncertain; however the multipotent stem cell theory applies best to this case. The most common staging system used is the two-stage system (limited-extensive). Because of the rarity of the disease, the management is extrapolated from that of SCLC. Limited-stage disease should be treated with etoposide-cisplatin chemotherapy in combination either with radiotherapy, or surgery or both. Extensive-stage disease should be managed by combined chemotherapy. Further research programmes are needed to improve the diagnosis and the treatment of SCCB tumour. This paper would provide a comprehensive review of the epidemiology, clinical features, diagnosis, pathologic features, histogenesis, molecular genetics, staging, treatment, and prognosis of SCCB.

Jacques, S. M., F. Qureshi, et al. (1998). "Interinstitutional surgical pathology review in gynecologic oncology: I. Cancer in endometrial curettings and biopsies." Int J Gynecol Pathol **17**(1): 36-41.

We report our experience with an interinstitutional surgical pathology review of endometrial curettings and biopsies originally diagnosed as cancer. Slides were reviewed from 182 women who were diagnosed with cancer and referred to our institution for further treatment; the slides had been sent for review at the request of the gynecologic oncologist. Review diagnoses were retrospectively compared to original diagnoses made on slides from these specimens, and significant discrepancies were identified in 43 (23.6%) of the 182 cases. For 16 (8.8%) patients, the diagnosis was downgraded from malignant to: 1) a benign non-hyperplastic process in 4 (2.2%); 2) scanty atypical glandular epithelium, not diagnostic for malignancy, in 2 (1.1%); and 3) endometrial hyperplasia in 10 (5.5%), including complex atypical hyperplasia in 8 (4.4%). Other significant differences involved histologic tumor classification in 16 (8.8%), degree of differentiation (two grades) in 2 (1.1%), determination of primary site in 4 (2.2%), and diagnosis of endocervical invasion in 5 (2.7%). Problems in comparison included lack of standardization of terminology and incomplete information from the original diagnoses. The high discrepancy rate between review and original diagnoses underscores the difficulty of interpreting these specimens. Review diagnoses of benign processes prevented an unnecessary operation for several women, and allowed those with cancer to undergo the most appropriate therapy. Review diagnoses in women with endometrial cancer contribute to quality medical care and have a major impact on a significant subset of patients.

Jacques, S. M., F. Qureshi, et al. (1998). "Interinstitutional surgical pathology review in gynecologic oncology: II. Endometrial cancer in hysterectomy specimens." Int J Gynecol Pathol **17**(1): 42-5.

During an 8-year period, 76 post-hysterectomy women with endometrial cancer were referred to our institution for evaluation or treatment, and had slides from the hysterectomy specimen sent for review at the request of the gynecologic oncologist (interinstitutional consultation). The original diagnosis was retrospectively compared to the review diagnosis and discrepancies were recorded. The most frequent discrepancy, identified in 24 (31.6%) of the 76 cases, involved assessment of myometrial invasion; 19 of these 24 had an original diagnosis of inner or middle third myometrial invasion and a review diagnosis of no myometrial invasion. The main reason for this discrepancy was irregularity of the endomyometrial junction, or, less commonly, extension of tumor into superficial adenomyosis. Additional discrepancies noted in 11 (14.4%) of the 76 cases included: 1) histologic tumor classification in 6 (7.9%); 2) assessment of angiolymphatic space invasion in 2 (2.6%); 3) identification of metastatic carcinoma in 1 (1.3%); and 4) change in diagnosis from adenocarcinoma to complex atypical hyperplasia and atypical polypoid adenomyoma in 1 each (2.6%). A significant subgroup of patients in this series had modifications in diagnosis; the most frequent discrepancy involved overdiagnosis of myometrial invasion, underscoring the difficulty sometimes encountered in this determination.

Jass, J. R., T. C. Smyrk, et al. (1994). "Pathology of hereditary non-polyposis colorectal cancer." Anticancer Res **14**(4B): 1631-4.

Pathological characteristics of colorectal cancers and adenomas developing in 140 members of 34 Hereditary Non-Polyposis Colorectal Cancer (HNPCC) families are described. In addition the pathological features of six cancers and 47 adenomas

obtained from 216 at risk subjects in colonoscopic surveillance programmes are given. Survival rates for Dukes A, B and C cancers were 90%, 76% and 50% respectively, but only 32% of cancers were Dukes C. This would support the view that HNPCC malignancies are relatively non-aggressive, despite there being an excess of poorly differentiated and mucinous tumours. There is circumstantial evidence that evolution of malignancy occurs through the adenoma - carcinoma sequence.

Jirstrom, K., L. Ryden, et al. (2005). "Pathology parameters and adjuvant tamoxifen response in a randomised premenopausal breast cancer trial." J Clin Pathol **58**(11): 1135-42.

BACKGROUND: Subgroups of breast cancer that have an impaired response to endocrine treatment, despite hormone receptor positivity, are still poorly defined. Breast cancer can be subdivided according to standard pathological parameters including histological type, grade, and assessment of proliferation. These parameters are the net result of combinations of genetic alterations effecting tumour behaviour and could potentially reflect subtypes that respond differently to endocrine treatment. AIMS: To investigate the usefulness of these parameters as predictors of the response to tamoxifen in premenopausal women with breast cancer. MATERIALS/METHODS: Clinically established pathological parameters were assessed and related to the tamoxifen response in 500 available tumour specimens from 564 premenopausal patients with breast cancer randomised to either two years of tamoxifen or no treatment with 14 years of follow up. Proliferation was further evaluated by immunohistochemical Ki-67 expression. RESULTS: Oestrogen receptor positive ductal carcinomas responded as expected to tamoxifen, whereas the difference in recurrence free survival between control and tamoxifen treated patients was less apparent in the relatively few lobular carcinomas. For histological grade, there was no obvious difference in treatment response between the groups. The relation between proliferation and tamoxifen response seemed to be more complex, with a clear response in tumours with high and low proliferation, whereas tumours with intermediate proliferation defined by Ki-67 responded more poorly. CONCLUSIONS: Clinically established pathology parameters seem to mirror the endocrine treatment response and could potentially be valuable in future treatment decisions for patients with breast cancer.

Junker, K., T. Wiethege, et al. (2000). "Pathology of small-cell lung cancer." J Cancer Res Clin Oncol **126**(7): 361-8.

The morphological differentiation between small-cell and non-small-cell lung cancer has great prognostic and therapeutic significance for the patient. Malignant lung tumors are now classified according to the new 1999 WHO/IASLC classification of lung and pleural tumors. The variant of heterogeneously differentiated "combined small-cell carcinoma" can be distinguished from classical small-cell carcinoma, whereas the subtype of "intermediate cell carcinoma" is no longer used. Together with "large-cell neuroendocrine carcinomas" and typical or atypical carcinoid tumors, small-cell lung cancers are currently histogenetically categorized as neuroendocrine lung tumors. In contrast to large-cell neuroendocrine carcinoma, the immunohistochemical demonstration of neuroendocrine differentiation is not a prerequisite for the diagnosis of small-cell lung cancer. Although electron-microscopical, immunohistochemical, and molecular-biological findings have considerably increased our understanding of the pathogenesis and progression of malignant lung tumors, routine pathological-anatomical diagnostics are still decisively based on light-microscopical evaluation of tissue samples.

Kaw, L. L., Jr., C. K. Punzalan, et al. (2002). "Surgical pathology of colorectal cancer in Filipinos: implications for clinical practice." J Am Coll Surg **195**(2): 188-95.

BACKGROUND: A number of studies published in the Philippine literature have demonstrated certain peculiar clinicopathologic characteristics of colorectal cancer among Filipinos. This study presents the latest data and analyzes their implications for clinical practice. STUDY DESIGN: The pathology reports of all patients who underwent operation for colorectal cancer at the Philippine General Hospital over a period of 7 years were reviewed. RESULTS: One thousand two hundred seventy-seven patients were included. The male to female ratio was almost 1:1. The majority of patients were in the sixth and seventh decades of life, with a mean age of 55.3 years. Patients 40 years of age and younger made up 17% of the total. The site of cancer in order of frequency was rectum (49.8%), left colon (27.9%), and right colon (21.4%). Cancers of the right colon were more common in women, and rectal cancers were more frequent in men. Seventy-six percent of the tumors were well to moderately differentiated adenocarcinomas, and 6.7% were poorly differentiated. Mucinous and signet ring carcinomas were found in 11% and 1% of cases, respectively. Forty-four percent of patients had localized disease at the time of operation, 54% had regional disease, and 2% had disseminated disease. Associated predisposing conditions noted were polyps (4.7%), schistosomiasis

(3%), and tuberculosis (1.5%). CONCLUSIONS: Colorectal cancer in Filipinos exhibits a number of unique clinicopathologic features, such as a higher proportion of early age of onset tumors, more advanced stage at presentation, an association with chronic granulomatous diseases, and relatively rare occurrence with polyps. This might suggest the possibility of a different pathway for tumor development of colorectal cancer in this population of patients. Also, current screening guidelines advocated for the Western population might not be appropriate for Filipinos.

Keating, J., S. Lolohea, et al. (2003). "Pathology reporting of rectal cancer: a national audit." N Z Med J **116**(1178): U514.

AIM: To audit the quality and completeness of histopathology reports of rectal cancer resections submitted to the National Cancer Registry in 2000. METHODS: All 388 mid- and low-rectal-cancer specimen reports submitted to the Registry were reviewed. Reports were scored according to a pre-defined 'proforma' as to the completeness of the pathological examination and the submitted report. RESULTS: Scores from teaching hospitals, public non-teaching hospitals and private laboratories did not differ significantly. Multiple staging systems were used in 40% of reports and no stage was allocated in 31% of reports. Circumferential margin involvement was recorded in 63% of reports. CONCLUSIONS: No significant differences exist in the quality of pathology reporting of rectal cancer between different laboratory types, either public or private. There is a lack of uniform reporting of rectal cancer stage, with multiple staging systems in use. Circumferential margin involvement is frequently omitted in spite of its documented value as an indicator of quality of rectal cancer surgery, as an important predictor of local recurrence, and its more-recently established value as a marker for distant metastasis and survival.

Kim, M. M. and J. A. Califano (2004). "Molecular pathology of head-and-neck cancer." Int J Cancer **112**(4): 545-53.

Each year approximately 40,000 people in the United States and 500,000 people worldwide are diagnosed with head-and-neck squamous cell carcinoma (HNSC). Although there have been significant improvements in the treatment of this disease, leading to decreased morbidity, over the past few decades the 5-year survival rate has remained largely unchanged at 50%. Genetic and epigenetic alterations as well as viral agents have been implicated in the development of head-and-neck cancer. Advances in our understanding of the molecular biology underlying these processes have spawned numerous, diverse strategies to exploit this understanding in applied pathology. Preliminary investigations have analyzed body fluids and margins for the presence of cancer cells. Specific molecular alterations have been associated with improved treatment response and prognosis. Molecular therapy has been shown to have some clinical efficacy in HNSC. Expression profiles may be generated for specific primary tumors and compared to known markers of disease. Improved molecular characterization of primary tumors, surgical margins and body fluids may allow clinicians to detect and treat earlier lesions, predict a tumor's response to treatment, tailor treatment to specific molecular alterations and ultimately improve clinical outcomes related to HNSC.

King, B. and J. Corry (2009). "Pathology reporting in head and neck cancer--snapshot of current status." Head Neck **31**(2): 227-31; discussion 232-3.

BACKGROUND: Currently there is no standardized head and neck pathology reporting system in Victoria, Australia. The aim of this study was to document deficiencies in head and neck pathology reports at our institution. METHODS: The pathology reports of all patients with head and neck squamous cell carcinoma (HNSCC) who presented to Peter MacCallum Cancer Centre for postoperative radiotherapy (PORT) between January 1, 2004, and March 31, 2006, were critically assessed for 16 key pathological items. RESULTS: Only 37% reports contained all the 16 items. The most commonly missing items were "diameter of the largest involved lymph node" (38%), "presence/absence of lymphovascular space invasion" (30%), "presence/absence of peri-neural invasion" (28%), "clearance of margins in millimeters" (27%), and "presence/absence of extracapsular extension" (27%). The most variable item was the clearance in millimeters used to determine "clear margins". CONCLUSIONS: Several of the most important pathological factors predicting locoregional relapse in HNSCC are currently the least reliably reported items in head and neck pathology reports.

King, P. M., J. M. Blazeby, et al. (2004). "Upper gastrointestinal cancer pathology reporting: a regional audit to compare standards with minimum datasets." J Clin Pathol **57**(7): 702-5.

AIMS: Accurate pathological (pTNM) staging of oesophageal and gastric cancer provides important prognostic information. The aim of this study was to compare the standard of pathology reporting of oesophageal and gastric cancer resections from a cancer network with standards set by the Royal College of Pathologists. METHODS: All reports for

oesophageal and gastric cancer resections from the five hospitals in the cancer network in 2001 were collected. Individual items of information were compared with minimum datasets provided by the Royal College of Pathologists. Items were classified as "complete", "partially complete", or "absent". RESULTS: One hundred and ten reports were audited (54 oesophageal and 56 gastric). Fourteen gastric and 17 oesophagectomy reports were over 75% complete. Clinically important missing data occurred most frequently for the pM component of TNM staging (pMx omitted in 87 reports) and completeness of resection expressed as a bold statement (absent in 50 reports). Twelve reports could not be classified because the specimen contained no residual tumour after neoadjuvant treatment. CONCLUSION: The use of a standard proforma for reporting upper gastrointestinal cancers based on a minimum dataset provided by the Royal College of Pathologists is recommended, with modifications to allow for specimens with no tumour after neoadjuvant treatment.

Kliesch, S., M. Bergmann, et al. (1997). "Semen parameters and testicular pathology in men with testicular cancer and contralateral carcinoma in situ or bilateral testicular malignancies." Hum Reprod **12**(12): 2830-5.

We evaluated 14 patients with bilateral testicular tumour, one-sided tumour and contralateral carcinoma in situ (CIS) of the testis or testis tumour in single testis with respect to their fertility. We analysed semen parameters, serum hormones [follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone], testicular sonography, testicular volumes and testicular histology prior to further anti-cancer treatment. Ten out of 14 patients showed normal or reduced sperm concentrations, while 4/14 patients were azoospermic. Serum FSH levels showed a significant negative correlation with sperm concentrations in patients with testicular malignancies ($r = -0.64$, $P = 0.025$). Testicular volumes revealed a significant positive correlation with semen parameters in patients with testes that were affected by CIS ($r = 0.733$, $P = 0.038$). We conclude that even bilateral testicular cancer and/or CIS do not preclude fertility and, therefore, patients should be offered andrological investigation and therapy, including possibly surveillance strategy or the chance for cryopreservation of the semen prior to further treatment in order to preserve their chances for paternity.

Knowles, M. A. (2001). "What we could do now: molecular pathology of bladder cancer." Mol Pathol **54**(4): 215-21.

There is much information on the genetic alterations that contribute to the development of bladder cancer. Because it is hypothesised that the genotype of the cancer cell plays a major role in determining phenotype, this genetic information should impact on clinical practice. To date however, this has not happened. Some of the alterations identified in bladder cancer have clear associations with outcome-for example, mutational inactivation of the cell cycle regulator proteins p53 and the retinoblastoma protein (Rb). However, as single markers, these events have insufficient predictive power to be applied in the management of individual patients. The use of panels of markers is a potential solution to this problem. Examples of suitable panels include those genes/proteins with known impact on specific cell cycle checkpoints or with impact on cellular phenotypes, such as immortalisation, invasion, or metastasis. To evaluate such marker panels, large tumour series will be needed-for example, archival samples from completed clinical trials. The use of these valuable resources will require coordination of sample provision. This might involve central collection and distribution of tissue blocks, sections, or tissue arrays and the provision of patient follow up information to laboratories participating in a study. With the availability of microarray technologies, including cDNA and comparative genomic hybridisation arrays, the transcriptome and genome of transitional cell carcinomas of different phenotypes can be compared and will undoubtedly provide a wealth of information with potential diagnostic and prognostic uses. Although these studies can be initiated using small local tissue collections, high quality collection of fresh tissues from new clinical trials will be crucial for proper evaluation of associations with clinical outcome. Funding for molecular pathological studies to date has been poor. To begin to translate molecular information from the laboratory to the clinic and to make maximum use of valuable urological patient resources in the UK, adequate funding and scientific energy are required. Whereas the latter is not in doubt, present funding for this type of translational research is inadequate.

Knuutila, S. (2004). "Cytogenetics and molecular pathology in cancer diagnostics." Ann Med **36**(3): 162-71.

The importance of cytogenetic and molecular genetic changes in cancer diagnostics has long been recognized. Especially chromosomal translocations have an established role in diagnosis, prognosis, and prediction of response to treatment in hematologic malignancies. Today some leukemias are classified according to cytogenetic changes. Characterized translocations have provided instrumental clues to

understanding of molecular mechanisms of cancer, which in turn have enabled development of molecularly targeted treatments. This paper reviews the diagnostic significance of novel cytogenetic and molecular genetic techniques in human malignancies. Not only in hematologic malignancies and sarcomas but also in neurogenic tumors and carcinomas numerous diagnostically, prognostically, predictively and therapeutically important genetic changes have been described over the past few years, and novel genetic markers are discovered at a rapidly growing rate. New methods and characterized specific genetic markers have opened a new era also in detection of minimal residual cells.

Kopald, K. H., J. R. Hiatt, et al. (1990). "The pathology of nonpalpable breast cancer." Am Surg **56**(12): 782-7.

A principal goal of mammographic screening is the early detection of breast cancer. We reviewed records of 125 women who were referred because of nonpalpable, suspicious abnormalities on mammogram, which subsequently proved to be cancer, requiring mammographic localization biopsy and subsequent surgery for therapy. We found that 72 (57.6%) had invasive tumors, 15 (12%) showed evidence of microinvasion and 38 (30.4%) were noninvasive. A total of 115 patients had lymphadenectomy as part of their definitive surgery. Nine (12.7%) of the patients with infiltrating tumors had between one and 10 malignant nodes on histologic section. None of the patients with noninvasive or microinvasive tumors were found to have involved nodes. The mammographic abnormalities which led to biopsy in our series were: calcifications in 74 (59.2%) patients, mass lesions in 39 (31.2%), mass lesions with calcifications in 11 (8.8%), and asymmetry in one (0.8%). Of the nine patients with nodal metastases, seven (77.8%) had a mass with or without calcifications as the indication for biopsy. Increasing tumor size was found to correlate with invasive tumors on histopathologic examination and the incidence of lymph node metastases. Thirty-seven (54.4%) of the patients with infiltrating tumors had a tumor size greater than 1 cm. Further, seven (77.8%) of the nine lymph node positive patients had tumors between 1 and 3 cm in size. Of note, however, is that two (22.2%) patients with microscopic tumors had involved nodes. The 4-year actuarial survival in patients with infiltrating tumors was 85.2 per cent, while that for patients with noninvasive or microinvasive tumors was 100 per cent (median follow-up of 20 months).(ABSTRACT TRUNCATED AT 250 WORDS)

Korenaga, D., A. Watanabe, et al. (1991). "Laser treatment for poor-risk patients with early gastric cancer: post treatment pathology." Eur J Surg Oncol **17**(3): 316-8.

Two patients with early gastric carcinoma and who were poor surgical risks underwent gastrectomy following repeated laser endoscopy. Pathological findings of the resected stomach were reviewed. Lesions in both patients were ulcerative, with evidence of destruction of the muscularis mucosae caused by laser irradiation. Complete coagulation did not occur in the case of infiltrative-type involvement of the submucosal layer. Gastrectomy was carried out when the clinical status improved and both patients are now cancer-free. We propose that laser treatment for early gastric cancer should be considered for poor-risk patients.

Kricker, A., B. Armstrong, et al. (1999). "An audit of breast cancer pathology reporting in Australia in 1995." Br J Cancer **80**(3-4): 563-8.

To measure the quality of pathology reporting of breast cancer and establish a baseline against which future changes can be measured, we audited item completeness in breast cancer reports in Australia in 1995 before the release of specific recommendations from the Australian Cancer Network. Tumour type and size were given in reports of invasive breast cancer for 93% of women, 70% had, in addition, grade and clearance of the margins while only 28% had all recommended information. The most complete items in reports were histological type of breast cancer (99.6% of cases), tumour size (94%, 95% confidence interval (CI) 92-95) and margins of excision (87%, 95% CI 85-89). Histological grade (84%, 95% CI 82-86 of cases) and presence or absence of ductal carcinoma in situ (DCIS) (79%, 95% CI 77-81) were less complete and vessel invasion (61%, 95% CI 58-63) and changes in non-neoplastic breast tissue adjacent to the breast cancer (68%, 95% CI 66-71) the least complete. Less than half the reports of DCIS reported on tumour size (49%, 95% CI 42-57), presence or absence of necrosis (41%, 95% CI 34-49) or nuclear grade (39%, 95% CI 31-46). Around 1500 reports were identified as issued by 147 laboratories and 392 pathologists; 69% of pathologists issued fewer than two reports a month in the audit. We concluded that infrequency of reporting may have contributed to incompleteness of reporting. In addition, we found significant variation across Australian states with some indication that reporting was consistently poor in one state. The audit highlighted areas for improvement for breast cancer reporting in Australia. Research evidence suggests that multifaceted strategies are needed to assist

practitioners with implementing more uniform reporting standards.

Krnjacki, L. J., P. D. Baade, et al. (2008). "Reliability of collecting colorectal cancer stage information from pathology reports and general practitioners in Queensland." Aust N Z J Public Health **32**(4): 378-82.

OBJECTIVE: To investigate the reliability of collecting colorectal stage information from pathology reports and general practitioners in Queensland, Australia. METHODS: A longitudinal study of colorectal cancer survivors conducted in 2003 and 2004 (n=1966, response rate=57%) obtained stage information from clinical specialists (n=1334), general practitioners (GP) (n=1417) and by extracting stage from pathology reports (n=1484). Reliability of stage information was determined by comparing stage from GPs and pathology reports with that reported by the clinical specialists, using a weighted kappa. RESULTS: GPs and pathology reports each had a similar level of agreement with clinical specialists, with kappa scores of 0.77 (0.75-0.80) (n=1042) and 0.78 (0.75-0.81) (n=1152), respectively. Results were similar when restricting to records staged by all three methods (n=847). GPs had similar levels of agreement with clinical specialists within each stage, although pathology reports tended to under-stage patients in Stage D (0.37). Collapsing stage into two categories (A or B, C or D) increased the reliability estimates from the pathology reports to 0.91 (0.88-0.93), but there was little change in GP estimates 0.79 (0.75-0.83). CONCLUSIONS: Extractions from pathology reports are a valid source of broad stage information for colorectal cancer. IMPLICATIONS: In the absence of clinical stage data, access to pathology records by population-based cancer registries enables a more accurate assessment of survival inequalities in colorectal cancer survival.

Kwon, J. S., J. A. Francis, et al. (2007). "When is a pathology review indicated in endometrial cancer?" Obstet Gynecol **110**(6): 1224-30.

OBJECTIVE: Discrepancies may exist between an original pathology report and formal pathology review, with subsequent implications for treatment. We conducted a study of pathology review in endometrial cancer from a population-based study to identify areas of discrepancy and effect on treatment. METHODS: This was a retrospective cohort study in Ontario, Canada from 1996 to 2000. We identified hysterectomy cases from patients with endometrial cancer that were subject to formal pathology review by a gynecologic pathologist at one of six tertiary care centers. Sarcomas and other rare histologic subtypes with fewer than five cases were excluded. We evaluated discrepancy between original pathology and review by demographics, stage, grade, and risk group. Four risk groups were defined: 1) low (stage I), 2) intermediate (stage I and II), 3) high-risk (stage I and II), and 4) advanced stage (all stage III and IV). Reclassification from one risk group to another upon pathology review represented a potential change in treatment. Factors associated with significant discrepancy were identified by a multivariable logistic regression model. RESULTS: Formal pathology review was available on 450 cases. There were no differences by age, year, or hospital type. The overall discrepancy rate was 42.7% (95% confidence interval 38.2-47.3%). The intermediate-risk group had the highest rate of reclassification into another group (33.1%). The most significant rates of discrepancy were associated with endometrioid grades 2 and 3 tumors and stage IIA disease (39.8%, 50.9%, and 79.6%, respectively). CONCLUSION: There was significant discrepancy between original pathology and formal review in endometrial cancer, with implications for guidelines on pathology review at a population level. LEVEL OF EVIDENCE: III

LaCasce, A. S., M. E. Kho, et al. (2008). "Comparison of referring and final pathology for patients with non-Hodgkin's lymphoma in the National Comprehensive Cancer Network." J Clin Oncol **26**(31): 5107-12.

PURPOSE: Before the implementation of the WHO lymphoma classification system, disagreement about pathologic diagnosis was common. We sought to estimate the impact of expert review in the modern era by comparing final pathologic diagnoses at five comprehensive cancer centers with diagnoses assigned at referring centers. PATIENTS AND METHODS: Patients in the National Comprehensive Cancer Network (NCCN) non-Hodgkin's lymphoma (NHL) database with a documented pathologic diagnosis before presentation and a final pathologic diagnosis of any of five common B-cell NHLs were eligible. After central review of discordant cases, we estimated the rate of pathologic concordance, then investigated the etiology of discordance as well its potential impact on prognosis and treatment. RESULTS: The overall pathologic discordance rate was 6% (43 of 731 patients; 95% CI, 4% to 8%). For the majority of cases in which the referring diagnosis was apparently final, no additional studies were conducted at the NCCN center, and the change in diagnosis reflected a different interpretation of existing data. Concordance was highest for diffuse large B-cell lymphoma (95%) and follicular lymphoma (FL; grades 1, 2, and not otherwise specified, 95%) and lowest for grade 3 FL (88%). Of the 43 pathologically discordant cases, 81% (35 patients) might have experienced a change in treatment as a result of the pathologic reclassification. CONCLUSION: In the era of the WHO lymphoma

classification system, the majority of common B-cell NHLs diagnosed in the community were unchanged by second opinion review by an expert hematopathologist. However, for one patient in 20, there was a discordance in diagnosis that could have altered therapy.

Lalloo, F. and D. G. Evans (1999). "The pathology of familial breast cancer: Clinical and genetic counselling implications of breast cancer pathology." Breast Cancer Res **1**(1): 48-51.

Approximately 5% of all breast cancers are due to one of the high-risk breast cancer genes BRCA1 and BRCA2, or possibly to a third or fourth moderate- to high-risk gene(s). A further proportion of cases arise in the presence of a less striking family history, with later average age at onset and lower penetrance: familial breast cancer. Bilaterality is a recognized feature of hereditary breast cancer. Cancers often present at an early age, with the contralateral risk high within 10 years. Proof that bilateral malignancies are separate primaries can be difficult histologically, however, especially within 3 years. The recent finding of specific pathological features related to BRCA1 and, to a lesser extent, BRCA2 mutations means that, in addition to bilaterality and family history, a pathological element can be entered into the risk calculation for the presence of BRCA1/BRCA2 mutations. This will facilitate the targeting of mutation testing to families in which a positive result is most likely, and may subsequently influence the clinical management of these families.

Lazcano-Ponce, E. C., J. F. Miquel, et al. (2001). "Epidemiology and molecular pathology of gallbladder cancer." CA Cancer J Clin **51**(6): 349-64.

Gallbladder cancer is usually associated with gallstone disease, late diagnosis, unsatisfactory treatment, and poor prognosis. We report here the worldwide geographical distribution of gallbladder cancer, review the main etiologic hypotheses, and provide some comments on perspectives for prevention. The highest incidence rate of gallbladder cancer is found among populations of the Andean area, North American Indians, and Mexican Americans. Gallbladder cancer is up to three times higher among women than men in all populations. The highest incidence rates in Europe are found in Poland, the Czech Republic, and Slovakia. Incidence rates in other regions of the world are relatively low. The highest mortality rates are also reported from South America, 3.5-15.5 per 100,000 among Chilean Mapuche Indians, Bolivians, and Chilean Hispanics. Intermediate rates, 3.7 to 9.1 per 100,000, are reported from Peru, Ecuador, Colombia, and Brazil. Mortality rates are low in North America, with the exception of high rates among American Indians in New Mexico (11.3 per 100,000) and among Mexican Americans. The main associated risk factors identified so far include cholelithiasis (especially untreated chronic symptomatic gallstones), obesity, reproductive factors, chronic infections of the gallbladder, and environmental exposure to specific chemicals. These suspected factors likely represent promoters of carcinogenesis. The main limitations of epidemiologic studies on gallbladder cancer are the small sample sizes and specific problems in quantifying exposure to putative risk factors. The natural history of gallbladder disease should be characterized to support the allocation of more resources for early treatment of symptomatic gallbladder disease in high-risk populations. Secondary prevention of gallbladder cancer could be effective if supported by cost-effective studies of prophylactic cholecystectomy among asymptomatic gallstone patients in high-risk areas.

Lee, F., D. B. Siders, et al. (1991). "Prostate cancer: transrectal ultrasound and pathology comparison. A preliminary study of outer gland (peripheral and central zones) and inner gland (transition zone) cancer." Cancer **67**(4 Suppl): 1132-42.

A study was conducted to compare results of transrectal ultrasound with pathologic findings on 116 patients who underwent radical prostatectomy for treatment of prostate cancer. In 96% (111 of 116), transrectal ultrasound guided biopsies of a hypoechoic lesion proved cancer; seven patients had known Stage A cancer; one patient had cancer detected by palpation and not detected by ultrasound. Cancers in the outer gland (peripheral and central zones) were compared with cancers in the inner gland (transition zone) by both ultrasound and pathology. Forty-eight percent (52 of 108) of cancers originating in the outer gland showed extraprostatic extension (Stage C disease). The primary sites of tumor escape from the outer gland were the prostatic capsule (38%), anterior fibromuscular stroma (5%), seminal vesicle (18%), the base of the gland at the neurovascular bundle (21%), and the apex (31%). Twenty-two percent (17 of 54) of cancers originating in the inner gland (transition zone) showed extraprostatic extension (Stage C disease). The primary sites of tumor escape from the inner gland were the anterior fibromuscular stroma (6%) and apex (11%). Both histologic and biologic differences between outer and inner gland cancers were found when tumor size was controlled. Gleason scores were significantly different for inner and outer gland cancers, with mean scores of 6.2 +/- 1.6 and 7.4 +/- 0.9, respectively. An odds ratio of 8.6 confirmed the increased risk of extraprostatic extension for outer

gland cancer. Outer gland cancers showed increased aggressive behavior of both histologic and biologic nature. The difference in biologic aggressiveness of outer and inner gland cancers has definite implications for treatment options. Use of other diagnostic parameters, such as DNA ploidy, may help to determine which cancers to treat and when to treat them; this may have more relevance for cancers originating in the inner gland. Strategic transrectal ultrasound guided biopsy affords accurate tumor mapping and staging when modes of internal spread and escape of cancer from both outer and inner gland are known. Thus, transrectal ultrasound may be our "window of observation" through which additional research may explain the histologic and biologic discrepancies between outer and inner gland cancers.

Leivo, I. (2006). "Insights into a complex group of neoplastic disease: advances in histopathologic classification and molecular pathology of salivary gland cancer." Acta Oncol **45**(6): 662-8.

Cancers of major and minor salivary glands represent a histopathologic challenge in two major respects. The first challenge is the complexity of morphologic features and overlapping of histologic patterns in the different tumor entities many of which are relatively rare. The number of separate tumor entities to be considered in differential diagnosis has greatly increased in the two latest WHO classification systems 12 (Table I). The second challenge is prognostication based on histopathology. The clinical experience is that behavior of some salivary gland carcinomas does not correlate well with their histopathologic classification, and that tumors classified within the same category may exhibit quite different clinical outcomes. However, recent advances in histopathological classification have been combined with new tools in immunohistochemical diagnosis and prognostication including cell-proliferation markers, myoepithelial antigens, matrix metalloproteinases, steroid receptors, growth factors and their receptors. These have improved our possibilities for more specific choices in the treatment of a variety of salivary gland carcinomas. This paper will give an overview on recent developments in histopathological classification, prognostication, and molecular pathology of salivary gland cancer.

Lemaitre, J., Z. Mansour, et al. (2006). "Bronchoplastic lobectomy: do early results depend on the underlying pathology? A comparison between typical carcinoids and primary lung cancer." Eur J Cardiothorac Surg **30**(1): 168-71.

BACKGROUND: This study evaluates the impact of the underlying disease upon the surgical outcome of bronchoplastic lobectomy, comparing typical carcinoid tumours with primary lung carcinoma. PATIENTS AND METHODS: This retrospective study includes 98 consecutive patients (78 males, 20 females). Eighteen patients had a typical carcinoid tumour (group 1), and 80 had a primary bronchial carcinoma (group2). Fifty-six patients underwent bronchoplasty with full sleeve resection (10 patients from group 1, 46 from group 2) and 42 patients had a bronchoplasty with bronchial wedge resection (8 from group 1 and 34 from group 2). Right upper lobectomy was the most common procedure. We compared demographic data, surgical indications, the type of bronchoplasty and postoperative complications. RESULTS: The average age in group 1 (38.5+/-16.3 years; range 15-77) was significantly lower than in group 2 (61.4+/-9.5 years; range 14-75) ($p<0.001$). There were no postoperative deaths. Procedure-specific complications (anastomotic dehiscence and atelectasis) were found in 7 patients (8.75%) in group 2 (of which, three had a combination of two of the above-mentioned complications) but none (0%) in group 1 ($p=0.23$). Seven patients from group 2 (8.75%) required treatment for a residual pneumothorax for none (0%) in group 1 ($p=0.23$). The mean duration for air leak was comparable in both groups ($p=0.366$). Three patients (16.67%) from group 1 had non-surgical complications compared to 17 (21.25%) in group 2 (of which, one had a combination of two non-surgical complications) ($p=0.35$). CONCLUSION: Bronchoplastic resection is a safe operation in patients with carcinoid tumours and should be the reference for treatment.

Lemmens, V. E., I. van Lijnschoten, et al. (2006). "Pathology practice patterns affect lymph node evaluation and outcome of colon cancer: a population-based study." Ann Oncol **17**(12): 1803-9.

BACKGROUND: A large variation in the number of nodes examined between patients, hospitals, and regions has been reported for patients with colon cancer. We studied determinants of this variation and its relation to survival in the south of The Netherlands. PATIENTS AND METHODS: All patients who underwent resection for stage I-III colon carcinoma diagnosed from 1999 to 2002 in the Eindhoven Cancer Registry area were included ($n = 2168$). Determinants of lymph node evaluation and their relationship to survival were assessed, including variation between the six departments of pathology. RESULTS: A median number of six lymph nodes per specimen had been examined. The median number for each department of pathology ranged from three to eight ($P < 0.0001$). After correction for relevant factors, this variation remained, resulting in differences in the proportion of N+ tumours between departments from 29% to 41% ($P < 0.0001$). The

number of nodes examined was positively associated with survival. Survival for node-negative patients differed between the departments of pathology (up to hazard ratio 1.5; P = 0.02). CONCLUSION: There was a large variation in lymph node evaluation between the departments of pathology, leading to differences in stage distribution and survival. Intervention strategies should be directed at nodal assessment.

Little, A. G., E. G. Gay, et al. (2007). "National survey of non-small cell lung cancer in the United States: epidemiology, pathology and patterns of care." Lung Cancer **57**(3): 253-60.

PURPOSE: To determine the epidemiology, pathology and patterns of care for patients with non-small cell lung cancer (NSCLC) in the United States. METHODS: In 2001 the National Cancer Data Base, under direction of the American College of Surgeons, conducted a patient care evaluation study in 719 hospitals. We collected information on patient demographics and histories, diagnostic and staging methods, pathology, and initial treatment. RESULTS: Information on 40,909 patients was obtained; 93% were smokers. Slightly more than half were older than 70 years; 58.5% were male and 35% had adenocarcinoma. Comorbid conditions were present in 71.8% and 22% had a prior malignancy. A chest CT scan was performed in 92% of patients and PET scans in 19.3%. Mediastinoscopy was performed in 20.3%. 67.2% of patients had Stage III or IV disease. More of the Hispanic, Asian or Black patients than White had Stage IV disease ($p<0.01$). Treatment was multimodality in a little over 30% of patients. Surgery alone was primarily utilized for patients in Stage I or II. Choice of treatment correlated more with stage and age than comorbidities. CONCLUSION: Our results substantiated the pattern of increasing proportions of women with NSCLC and the increasing frequency of adenocarcinoma. Most patients presented with Stage III or IV disease. Ethnic minorities were more likely to present in late stage disease than Whites. Treatment strategies depended more on stage and age than comorbid burden. Older patients were less likely to receive surgery and more likely to be treated with radiation only or have no treatment.

Maini, A., C. Archer, et al. (1997). "Comparative pathology of benign prostatic hyperplasia and prostate cancer." In Vivo **11**(4): 293-9.

Basic studies on the pathogenesis of prostate disease including hypertrophy and cancer have been difficult due to the lack of suitable animal models. Much effort has been directed to the development of appropriate animal models, and yet many obstacles still remain. Rodents do not develop spontaneous hypertrophy of the prostate, in fact the prostate atrophies with advancing age. Guinea pigs appear to be a good model to study the effect of hormones on the prostate gland. Microinvasive prostatic adenocarcinoma occurs spontaneously in various species of rodents, and can be induced by radiation, hormones and chemical carcinogens. The man and dog appear to be the only mammals which suffer naturally from the pathological processes of the prostate gland associated with aging. We review the currently available models for the study of benign, and malignant prostate disease and assess the strengths and weaknesses each for preclinical investigations.

Mandai, M., K. Yamaguchi, et al. (2009). "Ovarian cancer in endometriosis: molecular biology, pathology, and clinical management." Int J Clin Oncol **14**(5): 383-91.

Recent molecular and pathological evidence suggests that endometriosis is a monoclonal, neoplastic disease. Moreover, endometriosis serves as a precursor of ovarian cancer (endometriosis-associated ovarian cancer; EAOC), especially of the endometrioid and clear cell subtypes. Although a variety of molecular events, such as p53 alteration, PTEN silencing, K-ras mutations, and HNF-1 activation, have been identified in EAOC, its precise carcinogenic mechanism remains poorly understood. Our recent data indicate that microenvironmental factors, including oxidative stress and inflammation, play an important role in the carcinogenesis and phenotype of EAOC. The management of endometriosis from the standpoint of EAOC is not standardized yet. To this end, clarification of the precise natural course and the risk factors that contribute to malignant transformation remain important goals. Among the phenotypes of EAOC, clear cell carcinoma, seems to require a specific treatment strategy, including molecular targeting.

Marchevsky, A. M., S. Shah, et al. (1999). "Reasoning with uncertainty in pathology: artificial neural networks and logistic regression as tools for prediction of lymph node status in breast cancer patients." Mod Pathol **12**(5): 505-13.

Axillary lymph node status is an important prognostic feature for patients with breast cancer, but the therapeutic value of axillary lymphadenectomy is controversial. It would be useful to be able to predict the status of axillary lymph nodes before lymphadenectomy from prognostic features evaluated in a previous breast biopsy. This prediction would be useful to optimize the treatment of patients with breast cancer who are unlikely to have nodal metastases. We studied 279 patients with invasive breast carcinoma treated with modified radical mastectomy or with

lumpectomy combined with axillary lymph node dissection. Prognostic factors evaluated were age, histologic type of invasive tumor, presence of associated ductal and/or lobular carcinoma in situ, lesion size, histologic and nuclear grades, DNA index, presence of multiploidy by flow cytometric analysis, and immunocytochemical expression of estrogen and progesterone receptors, proliferating nuclear cell antigen, and HER-2/neu oncogene. Several probabilistic neural networks (NNs) with genetic algorithms were developed using prognostic features as input neurons and lymph node status (positive or negative) as output neurons. The data were also studied with multiple regression and logistic regression analysis. The best NN model trained with 224 cases using 19 input neurons. It classified correctly 49 (89.0%) of 55 unknown cases (specificity, 97.2%; sensitivity, 80.0%; positive predictive value, 93.8%; negative predictive value, 87.5%). Several statistically significant models could be fitted with both multiple regression and logistic regression. The logistic regression model fitted with 240 cases using 6 independent variables estimated correctly 26 (66%) of 39 holdout cases. NNs and logistic regression models offer potentially useful tools to estimate the status of axillary lymph nodes of breast cancer patients before axillary lymphadenectomy. Future prospective studies with larger groups of patients and perhaps better prognostic markers are needed before these predictive multivariate models become ready for clinical use.

Marcus, J. N., P. Watson, et al. (1994). "Pathology and heredity of breast cancer in younger women." J Natl Cancer Inst Monogr(16): 23-34.

The pathology of early-age onset breast cancer is considered here from three perspectives: 1) benign proliferative disease, 2) the cancers themselves, and 3) familial and hereditary breast cancer. Hereditary breast cancer, a subset of familial breast cancer featuring a strong autosomal dominant pedigree pattern and multiple primary cancers, has a strong predilection for younger women, accounting for about one half of breast cancers under age 30. With respect to benign proliferative disease, the increased relative risk of breast cancer associated with proliferative disease with atypia, about fourfold to fivefold for all ages, is doubled by the presence of a family history of breast cancer and amplified by young age. With respect to the carcinomas, the relative incidences of medullary carcinoma and ductal carcinoma in situ are increased in young women, while lobular and tubular carcinomas are decreased. Invasive breast cancer is higher grade and more proliferative in younger women, as measured by thymidine-labeling index, DNA flow cytometric S-phase fraction, and proliferation-associated proteins. The increased fraction of ductal carcinoma in situ and higher grade invasive cancers may help to account, respectively, for increased recurrence rates with conservative therapy, and more aggressive natural history in younger women. Familial breast cancers show trends for increased medullary type, but the effect is not independent of age. Weak associations of family history with tubular carcinoma have been reported, but data for associations with lobular carcinoma in situ and invasive lobular carcinoma are conflicting. Hereditary breast cancer as a class has higher tumor proliferation rates, an effect independent of age. Knowledge of the pathology and biomarker characteristics of BRCA1 gene-linked hereditary breast cancers, which account for a substantial fraction of breast cancers in younger women, should shed light on the nature of the responsible gene(s) and guide approaches to therapy and prophylaxis.

Masood, S. (2003). "The expanding role of pathologists in the diagnosis and management of breast cancer: Worldwide Excellence in Breast Pathology Program." Breast J **9 Suppl 2**: S94-7.

Pathology is the study of human illness and it involves the morphologic and biologic recognition of abnormalities that are associated with a disease. Breast pathology represents an excellent example of this discipline. By providing diagnostic information and by characterizing the biologic behavior of a breast lesion, a pathologist plays a critical role in a patient's life. Any mistake in this exercise is associated with serious consequences. In addition, there are many unresolved issues in breast pathology, which contribute to our limited understanding of the biology of breast cancer, variability in diagnostic criteria, and significant diversity in breast cancer management and therapy. Furthermore, breast pathology has remained an underrecognized discipline, and its importance in diagnosis and disease management is not fully realized. In order to better serve our patients, particularly medically underserved women and those living in countries with limited resources, we must place emphasis on effectively using the talent and expertise of pathologists around the globe. For example, to provide a cost-effective way to diagnose breast cancer, particularly at advanced stages, pathologists can sample lesions by fine-needle aspiration biopsy (FNAB), stain the resulting smears, and provide an immediate bedside diagnosis. This is a valid contribution; however, this exercise requires the availability of a pathologist with experience in breast cytopathology. Alternatively the pathologist may seek consultations from more experienced pathologists. Developing strategies to better recognize the importance of high-quality breast pathology services

and to train qualified and innovative breast pathologists is an ambitious task. The proposed Worldwide Excellence in Breast Pathology Program may provide such an opportunity.

Mazzucchelli, R., M. Scarpelli, et al. (2009). "Pathology of prostate cancer and focal therapy ('male lumpectomy')." Anticancer Res **29**(12): 5155-61.

Focal therapy of the prostate is defined as prostate gland ablation aiming at eradication of unifocal low-risk prostate cancer, and preserving uninvolved (peri-) prostatic tissue and therefore quality of life. The major arguments against focal therapy can be classified under the headings of understaging and multifocality. The argument of understaging highlights the importance of the occasional, but troublesome, finding of a large, extraprostatic or high-grade tumor (Gleason score > or = 7) in about a quarter of radical prostatectomy specimens removed from men initially classified as having a low-risk tumor. Indeed, 85% of all prostate cancer cases are multifocal. These concerns can be offset by additional testing: another biopsy, especially a transperineal mapping biopsy, and magnetic resonance imaging (MRI) of the prostate. The technology needed to ablate small regions or sectors of the prostate harboring a known cancer is rapidly becoming available. Cryotherapy is already being used and the preliminary data are encouraging, Ultrasound-guided high-intensity focused ultrasound (HIFU), photodynamic therapy using newly developed light-sensitizing agents, and MRI-guided HIFU are all promising new tools.

McKenna, R. J., Sr. (1994). "The abnormal mammogram radiographic findings, diagnostic options, pathology, and stage of cancer diagnosis." Cancer **74**(1 Suppl): 244-55.

An abnormal mammogram often will detect a mass, a cluster of calcifications, or both; these findings are not pathognomonic and require a tissue diagnosis to confirm the presence of invasive cancer, in situ cancer, or a nonmalignant process. Although mammography is very sensitive, its abnormalities may be nonspecific. Ultrasound may help to distinguish a cystic mass from a solid mass. The mammographic report should be concise and not vague and must provide the referring physician with clear information as to whether the test is normal, a biopsy must be performed on the abnormality, or the abnormality will be reviewed with a repeat X-ray examination in 6-month intervals until the nature of the abnormality is determined. A common error is to palpate a breast mass that is not visible on the mammogram (false negative) and assume that the mass is not cancerous. Reasonable interpretation of a mammographic abnormality must differentiate malignant disease from a variety of benign conditions and at the same time minimize the number of biopsies performed on a mammographic abnormality that proves to be benign. Asymptomatic breast cancer may be detected mammographically when screening mammography is used; five to seven cancers should be detected in each 1000 women when initially screened, and this incidence will decrease to 0.8-3.5 cancers per 1000 women screened, depending on their age. In recent reports, the detection of an in situ, or a Stage 0, breast cancer occurred in about 25% of the women screened. The earlier the stage, the better the prognosis and the more conservative the treatment options that may be offered to the patient. Every mammographic practice must be audited for quality control. Modern computer technology may make this effort less tedious and time-consuming than it was in the past.

Mikuz, G. (1997). "Pathology of prostate cancer. Old problems and new facts." Adv Clin Path **1**(1): 21-34.

Based on autopsy and epidemiologic data the lifetime risk of developing prostate cancer for a 50-year-old man is 42%, but only 9.5% will develop a clinically manifest disease and only 2.9% will die from this disease. The actual rate of carcinoma detection using PSA, digital rectal examination and transrectal ultrasound is 1%-3%. The majority of prostate carcinoma never progress to clinically significant disease, a minor portion remains confined to the prostate for many years and other carcinomas progress rapidly to a life threatening disease. The dilemma for clinicians and pathologists dealing with this tumor is how to distinguish these three biologically different types. Pathologists play an important role in preoperative diagnosis and in the postoperative prognosis oriented evaluation of the prostatectomy material. Volunteer PSA screening trials have led to an enormous increase in core-needle biopsies of the prostate. Since biopsies are often performed in men without palpable or ultrasound-visible nodules, are now faced with an increasing number of equivocal morphological features which can not be clearly defined, even with standardized criteria. Further investigations are also required to elucidate the clinical importance of PIN detection in biopsies. The heterogeneous histomorphology of prostate carcinoma can not be used as a prognostic factor. Therefore the histological grading is a very important factor for the assessment of prognosis. Carcinoma grading in biopsies is also of limited value in predicting tumor stage. Currently, several different grading systems are in use. Gleason's grading is the most favored, although its reproducibility is very low. The stage of the prostate carcinoma is still the best prognostic factor. In order to accurately assess the

pTNM stage, TUR or prostatectomy material must be subject to extensive and standardized processing. Additionally, the volume of the tumor, the vascular invasion, the amount of extension of the tumor through the prostate capsule and perhaps the neoangiogenesis might be valid prognostic factors for disease progress and for survival. The value of novel methods (p53, bcl-2, apoptosis, microvessel density, interphase cytogenetics, androgen receptor mutation, neuroendocrine cells, E-Cadherin) remains to be proved. DNA ploidy is a good prognostic factor after prostatectomy and can be used to plan adjuvant hormone therapy.

Minardi, D., A. B. Galosi, et al. (2001). "Diagnostic accuracy of percent free prostate-specific antigen in prostatic pathology and its usefulness in monitoring prostatic cancer patients." Urol Int **67**(4): 272-82.

INTRODUCTION: The aim of our study was to evaluate the clinical usefulness of percent free prostate-specific antigen (PSA) [ratio of free PSA (fPSA) to total PSA (tPSA); f/tPSA] in prostatic pathology and its usefulness in monitoring prostatic cancer patients. PATIENTS AND METHODS: Our prospective study was carried out on 470 consecutive male patients referred to our outpatient urological clinic for observation. We looked for relationships between tPSA, fPSA and percent free PSA and the patient's age, prostatic volume and histologic diagnosis as assessed by prostatic biopsies or surgical specimens (benign prostatic hypertrophy, carcinoma, hypertrophy with inflammation). In all cases, we calculated the specificity, sensitivity and diagnostic accuracy of percent free PSA in the diagnosis of prostatic diseases, using cutoff values ranging from 14 to 20%. In prostatic cancer patients, we considered the relationships between the various PSA molecular forms and staging, grading and follow-up values. We also evaluated the effects of hormonosuppressive therapy on the serum markers and noted for which tPSA value percent free PSA possessed the greatest diagnostic accuracy. RESULTS: While tPSA and fPSA values appeared to be correlated with patient age and prostatic volume, percent free PSA did not show a relationship with these parameters. The specificity, sensitivity and overall diagnostic accuracy were better assuming a 16% cutoff value for percent free PSA than with other cutoff values. Prostatic inflammation associated with benign hypertrophy can cause false positives in both tPSA and f/tPSA measurements, since 60% of these patients have an f/tPSA ratio below 16%. In diagnosing carcinoma, the diagnostic accuracy of percent free PSA is 100% when tPSA is between 2.5 and 4.0 ng/ml. Percent free PSA is not linked with staging in prostatic cancer, but it does appear to be related to the Gleason score. In patients receiving hormonosuppressive treatment, f/tPSA decreased significantly, and more so in patients with a higher Gleason score. In patients with disease in rapid progression, percent free PSA was lower than in patients in a stable condition. CONCLUSIONS: Based on our experience, 16% as the f/tPSA cutoff value for discriminating between benign and malignant pathologies is the best possible choice, as it provides the highest overall values of sensitivity, specificity and diagnostic accuracy (80, 61.5 and 84.5%, respectively) in the diagnosis of prostatic cancer. We believe that f/tPSA is not a definitive test for diagnosing prostatic cancer. Our observations on the behavior of percent free PSA in relation to prostatic carcinoma grading and staging and in the follow-up of carcinoma patients are interesting; however, further studies are needed to define the appropriate role of f/tPSA in patients with an established diagnosis of prostatic carcinoma and in the follow-up of patients with prostatic cancer.

Morris, E. J., N. J. Maughan, et al. (2007). "Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer? The need for high quality pathology." Gut **56**(10): 1419-25.

OBJECTIVE: To identify by routine pathology which Dukes B colorectal cancer patients may benefit from chemotherapy. METHOD: Retrospective study of the five year survival of colorectal cancer patients for whom colorectal pathology minimum datasets had been collected between 1997 and 2000 in the Yorkshire region of the UK. The study population consisted of 1625 Dukes B and 480 Dukes C patients who possessed one positive node treated between 1997 and 2000. The predictive ability of the Petersen prognostic model was investigated and survival of Dukes B patients with potentially high risk pathological features was compared to that of Dukes C patients with one positive node. RESULTS: Only 23.3% of patients had all the pathological variables required for the application of Petersen's index reported. The index offered a statistically significant survival difference of 24.3% and 30.3% between high and low risk colon ($p<0.01$) and rectal cancer patients ($p<0.01$). The size of these effects was smaller than predicted by the original model. Survival of Dukes B patients with any of the high risk pathological factors or low nodal yields was lower than that of Dukes C patients who possessed one positive node. CONCLUSION: Petersen's index discriminated between high and low risk Dukes B colorectal tumours, but inadequate pathological reporting diminished its ability to identify all high risk patients. The survival of patients with any high risk feature was lower than the threshold for adjuvant therapy of one lymph node positive Dukes C

colorectal cancer. Chemotherapy may benefit patients with such features. Improving the quality of pathological reporting is vital if high risk patients are to be reliably identified.

Mostofi, F. K., G. P. Murphy, et al. (1995). "Pathology review in an early prostate cancer detection program: results from the American Cancer Society-National Prostate Cancer Detection Project." Prostate **27**(1): 7-12.

Biopsy materials obtained in the American Cancer Society National Prostate Cancer Detection Project were reviewed at the Central Pathology Laboratory at the Armed Forces Institute of Pathology. Of 265 cases submitted, 177 were diagnosed as prostatic carcinoma, 7 as prostatic intraepithelial neoplasia (PIN), 13 as atypical glands or atypical hyperplasia, and the remaining 68 were benign hyperplasias. Irrespective of the means of detectin or the grading system used (Gleason or WHO-Mostofi), a large majority of the cancers were detected as low-grade tumors. Of 27 cases of PIN reported, 20 were associated with cancer, leaving 7 cases with the sole diagnosis of PIN. These data may indicate the increased use of prostate-specific antigen (PSA), digital rectal examination (DRE), and transrectal ultrasound (TRUS) in the United States is shifting the spectrum of prostate cancer pathology toward early low-grade tumors.

Murphy, W. M. (1998). "The Current Status of the Pathology of Prostate Cancer." Cancer Control **5**(6): 500-506.

BACKGROUND: The pathology of prostate cancer in modern day medicine cannot be understood simply in terms of tissue patterns or genetic abnormalities. Efforts to accommodate changes in patient care delivery and reimbursement, combined with an explosion in information, have wrought major changes in pathology. METHODS: The author summarizes the current status of the pathology of prostate cancer in light of these influences. The detection of prostate cancer in needle biopsies, the diagnostic interpretations that tend to confuse clinicians, the prognostic factors in prostate cancer, and the effects of radiotherapy and hormone therapy on prostatic tissue are discussed. RESULTS: Collegial associations are difficult to maintain when consultants are spatially separated and patients are shuttled between primary care and specialty centers. Economic forces cannot be ignored, regardless of the level of altruism of individual practitioners. A medical environment governed by judgment and wisdom is difficult to maintain when external forces and even patients themselves demand application of the latest information to each case. CONCLUSIONS: Current trends in medicine offer almost as many pitfalls as promises. Information gathering and transfer tend to marginalize anatomic pathologists from patient care. Current pathology is affected by the influences of medicolegal and economic forces.

Naito, S., K. Kuroiwa, et al. (2008). "Validation of Partin tables and development of a preoperative nomogram for Japanese patients with clinically localized prostate cancer using 2005 International Society of Urological Pathology consensus on Gleason grading: data from the Clinicopathological Research Group for Localized Prostate Cancer." J Urol **180**(3): 904-9; discussion 909-10.

PURPOSE: We validated the 2001 Partin tables and developed an original nomogram for Japanese patients using the 2005 International Society of Urological Pathology consensus on Gleason grading. MATERIALS AND METHODS: Prostatectomy specimens from 1,188 Japanese men who underwent radical prostatectomy for clinically localized prostate cancer (cT1-2) between 1997 and 2005 were analyzed. Polychotomous logistic regression analysis was used to construct a nomogram to predict final pathological stage (organ confined disease, extraprostatic extension, seminal vesicle invasion and lymph node involvement) from 3 variables, including serum prostate specific antigen, clinical stage and biopsy Gleason score. The area under the ROC curve was used to compare the new nomogram with the Partin tables. RESULTS: Preoperative serum prostate specific antigen and biopsy Gleason score were higher in the Japanese cohort than in the Partin cohort. The distribution of clinical and final pathological stages was similar in the 2 cohorts. The AUC for predicting organ confined disease was 0.699 and 0.717 for data applied to the Partin tables and to the new nomogram, respectively. The AUC for predicting lymph node involvement was 0.793 and 0.863, respectively. CONCLUSIONS: To our knowledge this is the first preoperative nomogram developed for clinically localized prostate cancer in Japanese patients. Although the new nomogram predicted the pathological stage of prostate cancer in Japanese patients more accurately than the Partin tables, it did not satisfactorily predict organ confined disease. However, other predictive variables, such as more detailed pathological features of biopsy specimens or magnetic resonance imaging, may further improve prediction accuracy.

Nakhleh, R. E. and R. J. Zarbo (2001). "Surgical pathology-based outcomes assessment of breast cancer early diagnosis: a College of American Pathologists Q-Probes study in 199 institutions." Arch Pathol Lab Med **125**(3): 325-31.

OBJECTIVE: To develop breast cancer outcomes data relating pathologic tumor variables at diagnosis with clinical method of detection. DESIGN: Anatomic pathologists assessed 30 consecutive breast cancers at each institution, resulting in an aggregate database of 4232 breast cancers. SETTING: Hospital-based laboratories from the United States (98%), Canada, Australia, and Belgium. PARTICIPANTS: One hundred ninety-nine laboratories in the 1999 College of American Pathologists Q-Probes voluntary quality improvement program. MAIN OUTCOME MEASURES: Pathologic variables indicative of favorable outcomes included percentage of carcinomas detected at the in situ stage, tumors < or = 1 cm in diameter, and invasive cancers with lymph nodes negative for metastases. RESULTS: All outcomes measures, including percent in situ carcinomas (26.9% vs 13.8%), tumor size < or = 1 cm (57.8% vs 36.5%), and lymph node-negative status (77.8% vs 64%), were more favorable when tumors were detected by screening mammography (P <.001) compared to all other detection methods. CONCLUSIONS: This study demonstrates an opportunity for pathologists to develop outcomes information of interest to health care organizations, providers, patients, and payers by integrating routine oncologic surgical pathology and clinical breast cancer detection data. Such readily obtained interim outcomes data trended and benchmarked over time can demonstrate the relative clinical efficacy of preventive breast care provided by health care systems long before mortality data are available.

Niedzwiecki, S., K. Kuzdak, et al. (2007). "Normocalcemic, subclinical, asymptomatic primary hyperparathyroidism in patients with goiter or papillary thyroid cancer--preliminary report. Normocalcemic primary hyperparathyroidism and thyroid pathology." Wiad Lek **60**(5-6): 228-30.

The aim of the prospective study was the evaluation of primary, subclinical, normocalcemic hyperparathyroidism (PHPT) incidence in patients, operated on because of non-toxic (NTG), toxic (TG) goiter and papillary thyroid cancer (PTC). MATERIAL AND METHODS: The study was performed in the group of 196 patients operated on NTG (115 patients), TG (43 patients) and PTC (38 patients). All patients had never been operated because of goiter. No patient had clinical symptoms of PHPT. Calcium concentration (Ca), phosphorus concentration (P) and alkaline phosphatase activity (ALP) in blood serum were measured in all patients a day before operation. When those parameters were out of range, parathormone concentration (PTH) in blood serum was measured. In the case of elevated PTH concentration PHPT was diagnosed. Furthermore, in order to exclude renal failure and insufficiency tests for creatinine and urea concentrations in blood serum and urinalysis were performed. RESULTS: There was no case of increased Ca concentration among 158 patients with benign goiter. The values of at least one measured parameters (P or ALP) were abnormal in 47 out of 158 patients with benign goiter (29.7%). Increased PTH concentration (mean 101.5 pg/ml) was in 16 of 47 patients (10.1% of 158 patients). Normocalcemic PHPT was diagnosed in 12 (10.4%) NTG patients and 4 (9.3%) TG patients. In patients with PTC hypercalcemia was not affirmed. In 7 (18.42%) cases of 38 PTC patients P concentration and ALP activity were abnormal. Increased PTH concentration (84.85 pg/ml) was found in one female with PTC with normal values of P and ALP. Incidence of PHPT was observed in 2.63% of PTC patients. CONCLUSIONS: 1. There was no significant difference of PHPT incidence between various type of goiter. 2. In our study coexistence of PTC and normocalcemic, asymptomatic PHPT is rare.

Nutis, M., K. M. Garcia, et al. (2008). "Use of ultrasonographic cut point for diagnosing endometrial pathology in postmenopausal women with multiple risk factors for endometrial cancer." J Reprod Med **53**(10): 755-9.

OBJECTIVE: To determine if the established endometrial thickness cut point (5 mm) for abnormal endometrial pathology shifts to higher thickness in the presence of selected risk factors/comorbidities. STUDY DESIGN: A sample of 112 postmenopausal women was identified. The outcome was abnormal endometrial pathology, be it endometrial cancer or hyperplasia with atypia. Logistic regression was used to calculate prevalence odds ratios (ORs) of abnormal results for women with thick or thin endometria and 0 or > or = 1 of the following comorbidities/cofactors: obesity, diabetes, hypertension and use of hormone replacement therapy. RESULTS: Approximately half the sample was hypertensive; 56.3% were obese. A large proportion (84.8%) of the patients had > or = 1 of the comorbidities/cofactors of interest. Women with endometria > or = 12 mm and > or = 1 comorbidities appeared to have 5 times the odds of having an abnormal result compared to women with thin endometria (<12 mm) who had 0 comorbidities; this result was not statistically significant (adjusted OR = 5.08, p = 0.07). A dose-response curve (regression spline) showed that the prevalence of an abnormal outcome increased sharply between 5 and 9 mm. CONCLUSION: Clinicians should continue to use the 5-mm cut point when deciding whether patients should have endometrial sampling.

Oliveira, C., H. Moreira, et al. (2005). "Role of pathology in the identification of hereditary diffuse gastric cancer: report of a Portuguese family." Virchows Arch **446**(2): 181-4.

Mutations in E-cadherin gene are the underlying genetic defect in approximately one-third of the hereditary diffuse gastric cancer (HDGC) families described to date. Positive family history of diffuse gastric cancer and early age of onset of gastric tumours are the clinical criteria currently used to qualify for HDGC. In the present study, we describe a Portuguese family with HDGC that was selected for CDH1 mutation screening after histological observation of the gastrectomy specimen of one member, who died at the age of 23 years from widely invasive diffuse gastric carcinoma. The detection in the surgical specimen of tiny foci of intramucosal diffuse carcinoma as well as in situ carcinoma lesions and pagetoid spread of signet ring cells raised the hypothesis of HDGC, which was confirmed by pedigree analysis of the family and detection of CDH1 germline mutation. We conclude that there are morphological hints that may help in the identification of HDGC.

Oliveira, C., R. Seruca, et al. (2006). "Genetics, pathology, and clinics of familial gastric cancer." Int J Surg Pathol **14**(1): 21-33.

Gastric cancer is relatively common worldwide, mainly in its sporadic form, but familial aggregation of the disease may be seen in approximately 10% of the cases. This suggests a genetic cause for the cancer in those families that has not been identified in most cases. Despite all efforts to determine its genetic basis, a single syndrome has been characterized-the hereditary diffuse gastric cancer (HDGC)-which is specifically associated with CDH1 (E-cadherin) germline mutations in one third of the families. The other two thirds and all the gastric cancer families not fulfilling the HDGC criteria remain without molecular diagnosis. In this article we review the state of the art of familial gastric cancer regarding the molecular aspects, the clinical criteria, the pathology features, and the management recommendations described so far to be associated with this cancer disease.

Olivier, M., A. Petitjean, et al. (2009). "Somatic mutation databases as tools for molecular epidemiology and molecular pathology of cancer: proposed guidelines for improving data collection, distribution, and integration." Hum Mutat **30**(3): 275-82.

There are currently less than 40 locus-specific databases (LSDBs) and one large general database that curate data on somatic mutations in human cancer genes. These databases have different scope and use different annotation standards and database systems, resulting in duplicated efforts in data curation, and making it difficult for users to find clear and consistent information. As data related to somatic mutations are generated at an increasing pace it is urgent to create a framework for improving the collecting of this information and making it more accessible to clinicians, scientists, and epidemiologists to facilitate research on biomarkers. Here we propose a data flow for improving the connectivity between existing databases and we provide practical guidelines for data reporting, database contents, and annotation standards. These proposals are based on common standards recommended by the Human Genome Variation Society (HGVS) with additions related to specific requirements of somatic mutations in cancer. Indeed, somatic mutations may be used in molecular pathology and clinical studies to characterize tumor types, help treatment choice, predict response to treatment and patient outcome, or in epidemiological studies as markers for tumor etiology or exposure assessment. Thus, specific annotations are required to cover these diverse research topics. This initiative is meant to promote collaboration and discussion on these issues and the development of adequate resources that would avoid the loss of extremely valuable information generated by years of basic and clinical research.

Onesti, J. K., B. E. Mangus, et al. (2008). "Breast cancer tumor size: correlation between magnetic resonance imaging and pathology measurements." Am J Surg **196**(6): 844-48; discussion 849-50.

BACKGROUND: As physicians increasingly use magnetic resonance imaging (MRI) for the evaluation of newly diagnosed breast cancers, a review of the correlation between MRI and pathology tumor size is imperative. METHODS: A retrospective review of 91 breast tumors comparing preoperative MRI tumor size to final pathology tumor size was performed. RESULTS: MRI and pathology tumor size were positively correlated (R = .650), but with an average overestimation by MRI of .63 cm (P <.0001). When stratified by MRI tumor size (< or = 2.0 cm and > 2.0 cm), a significant difference was found only in tumors greater than 2.0 cm (average overestimation = 1.06 cm; P <.0001). This trend continued for the histological subtypes of ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), and invasive lobular carcinoma (ILC). CONCLUSIONS: MRI tumor size correlates with pathology size; however, a significant overestimation exists, particularly for tumors > 2.0 cm. Clinicians should therefore use caution in relying on MRI tumor size in

determining candidacy for breast conservation therapy (BCT).

Ono, H. (2006). "Early gastric cancer: diagnosis, pathology, treatment techniques and treatment outcomes." Eur J Gastroenterol Hepatol **18**(8): 863-6.

Recent improvements in endoscopic techniques and technologies and an increased understanding and recognition of the importance of early gastric cancer (EGC) will result in increases in the detection and diagnosis of precancerous or early cancerous lesions. The incidences of nodal metastasis of intramucosal and submucosal EGC are 3 and 20%, respectively. Therefore, major surgery may be inappropriate in many of these patients, and many cases of EGC may be treated by endoscopic mucosal resection (EMR). EMR was first introduced in Japan 20 years ago. Most EMR have been performed by the so-called 'strip biopsy' or EMR-C methods. However, we have sometimes experienced local recurrence in cases that had been resected in multiple fragments by these methods. To obtain 'complete resection', we developed the endoscopic submucosal dissection (ESD) technique using a special endoscopic knife, the insulation-tipped diathermic knife (IT knife). The rate of complete resection, i.e. cut margin free from cancer and one-piece resection, was remarkably higher for the IT knife technique than conventional EMR. ESD cases are increasing rapidly in Japan. EMR including ESD is a good method for patients with gastric cancer to preserve the stomach. For EMR, it is necessary to find EGC. Both diagnosis and treatment are important, and scientific data regarding lymph node metastasis and clinicopathological features are required.

Opolski, A., M. Mazurkiewicz, et al. (2000). "The role of GABA-ergic system in human mammary gland pathology and in growth of transplantable murine mammary cancer." J Exp Clin Cancer Res **19**(3): 383-90.

In this paper we described the results of our studies on the baclophen (gamma aminobutyric acid (GABA)-B receptor agonist) inhibitory effect on the growth of experimental mammary cancer 16/C in mice and on the estimation of GABA level and GAD (glutamine acid decarboxylase--the key enzyme in GABA synthesis) activity after this treatment in mice. The experimental data are confronted with the estimation of GABA level and GAD activity in human mammary gland material taken from the patients with benign breast tumors of different pathological and age related hormonal stages. A significant inhibition of 16/C tumor growth in treated with baclophen mice was observed. Mean GABA level and GAD activity were significantly higher both in tumor and in normal tissue of baclophen treated mice in comparison to control animals. The results of clinical studies have shown that the lowest GABA level and GAD activity in tumor and normal mammary gland tissue was detected in patients in peri-menopausal stage. Both, in human and mouse material, the GABA level and GAD activity were higher in tumor than in normal tissue and there was a clear positive correlation between GABA level and GAD activity in both tissues studied. GABA level and GAD activity in tumor and in normal tissue were lower in patients with dysplasia than in patients with fibroadenoma. Considering our results, namely an inhibitory effect of GABA receptor agonist on mammary cancer growth and the correlation between GABA level and the stage of breast pathology and/or hormonal activity, it seems probable that GABA-ergic system is involved in hormonal regulation and pathogenesis of breast cancer.

Osin, P., J. Shipley, et al. (1998). "Experimental pathology and breast cancer genetics: new technologies." Recent Results Cancer Res **152**: 35-48.

The goal is to understand the critical events in tumour development and to apply this understanding to new approaches to diagnosis, prevention and treatment. It is clear that breast cancer is a heterogeneous disease at the molecular level, raising the possibility of a future functional classification based on mechanisms rather than morphology. These molecular phenotypes will also confer predictive value on the potential of the tumour to invade, metastasise and respond to or resist new therapeutic strategies. Studies of the genome in individuals are predicted also to enable the identification of polymorphisms that are associated with increased susceptibility to environmental factors, in addition to possibly explaining de novo variations in responses to drugs and radiation. The difficulty is how to identify which, of the approximately 30,000 genes expressed by a typical cancer cell alone or in combination, are the ones involved in these processes. The majority of breast cancers have such a multitude of molecular changes that it is difficult to distinguish between those that are critical to tumour progression and those that are epiphenomena of genetic instability and abnormalities in DNA repair. The identification of the earliest events in carcinogenesis must be the best hope, as it will then be possible to target the events that predispose to other secondary changes before they occur. Genomics and proteomics is the current hope to take us forward. This involves the application of a number of new technologies to facilitate the profiling of individual tumours, including laser-guided microdissection of microscopic lesions, comparative genomic hybridisation and loss of heterozygosity analysis of DNA using microarray technology to study DNA and expressed RNAs and protein profiling using

2D gel mass spectroscopy. With over 100,000 mRNAs and proteins to examine in complex tissues and in various combinations, there is obviously going to be a requirement for a large investment in computing power (bioinformatics) to facilitate the analysis of these data in relation to the clinical characteristics of the individual tumour and the patient.

Ozsener, S., A. Ozaran, et al. (1998). "Endometrial pathology of 104 postmenopausal breast cancer patients treated with tamoxifen." Eur J Gynaecol Oncol **19**(6): 580-3.

OBJECTIVE: To investigate the effects of tamoxifen on the endometrium in postmenopausal breast cancer patients. METHODS: Endometrial thickness was measured by transvaginal sonography and endometrial biopsies were done in 104 postmenopausal breast cancer cases who were treated with tamoxifen. Histopathologic findings were discussed. RESULTS: Mean endometrial thickness was 11.7+/-5.9 mm and duration of tamoxifen administration was 35.3 months. Four endometrial cancers, 17 endometrial hyperplasias, 25 proliferative endometrium, 5 endometrial polyps in the endometrial biopsies. We observed atrophic endometrium in 53 of the cases. Only one case with endometrial polyps was observed as a premalignant lesion when the endometrium was less than 5 mm, 51% of the cases had thicker endometrium (more than 10 mm) and 32% of these cases had malignant and premalignant endometrium. We found a significant correlation with the duration of tamoxifen and age ($p<0.05$). One hundred and two of our cases were asymptomatic; only 2 out of 4 endometrial cancer cases had vaginal spotting. A significant relation was noticed between endometrial thickness and duration of tamoxifen treatment ($p=0.025$). CONCLUSION: It was concluded that positive endometrial findings and endometrial thickness were due to continuous unopposed tamoxifen treatment and our findings support the hypothesis that tamoxifen increases the risk of endometrial carcinoma and premalignant changes.

Pai, S. I. and W. H. Westra (2009). "Molecular pathology of head and neck cancer: implications for diagnosis, prognosis, and treatment." Annu Rev Pathol **4**: 49-70.

The prototypic head and neck squamous cell carcinoma (HNSCC) arises from the mucosal lining of the upper aerodigestive tract, demonstrates squamous differentiation microscopically, involves older men with a long history of cigarette smoking and alcohol consumption, and is treated by multimodality therapy. HNSCC has long been regarded as a uniform disease process requiring a methodical and unwavering therapeutic approach. Divergence in epidemiologic trends among HNSCCs arising from different anatomic sites has introduced a view that, morphologic repetition aside, head and neck cancers form a heterogeneous group. This view has been supported at the molecular genetic level. A more complete understanding of the molecular genetics of head and neck cancer is providing new insights into long-held but poorly comprehended concepts such as field cancerization and is introducing various biomarkers with potential application for diagnosing, staging, monitoring, and prognosticating HNSCC.

Paley, P. J. (2002). "Angiogenesis in ovarian cancer: molecular pathology and therapeutic strategies." Curr Oncol Rep **4**(2): 165-74.

Ovarian cancer claims the lives of more women in North America each year than all other gynecologic malignancies combined. Despite the high initial response rates of patients with advanced ovarian cancer to aggressive primary surgical debulking followed by combination chemotherapy, the majority of patients will ultimately develop disease recurrence. The high risk of relapse and nearly guaranteed incurability after relapse is due to genetic instability and a high mutation rate of neoplastic cells that together allow for a high risk of selection for drug resistance. Given the seemingly insurmountable obstacle that acquired drug resistance presents in a setting of minimal, often undetectable, residual tumor burden in women with ovarian cancer, antiangiogenic-targeted therapies offer an attractive strategy for enhanced long-term disease-free survival. The past decade has witnessed a substantial proliferation in our knowledge regarding tumor angiogenesis, which has spurred interest in antiangiogenesis drug development. Current clinical trials are evaluating these agents in a variety of solid tumors, including ovarian cancer. Preliminary work has provided hope that the addition of antiangiogenic therapies may be incorporated into the treatment of women afflicted with ovarian cancer and may translate into enhanced survival.

Paramo, J. C. and G. Gomez (1999). "Dynamic CT in the preoperative evaluation of patients with gastric cancer: correlation with surgical findings and pathology." Ann Surg Oncol **6**(4): 379-84.

BACKGROUND: The use of diagnostic techniques in the preoperative staging of patients with gastric cancer must be better defined. To further clarify which technique is indicated, we applied a new modality of computed tomography (CT) scanning for patients with gastric cancer. METHODS: Dynamic CT of the abdomen using water as oral contrast agent was performed in 30 patients with gastric

adenocarcinoma. Patients without evidence of metastatic disease underwent exploratory laparotomy and intraoperative staging. Resectable patients had surgical excision and definitive pathologic staging. RESULTS: Two patients (7%) had metastatic disease by CT and were considered inoperable. The remaining 28 underwent laparotomy. Of these, six (21%) were unresectable and 22 (79%) had surgical resection. Dynamic CT adequately suggested advanced stage disease in four (67%) of the 6 unresectable patients. Wall thickness in dynamic CT correlated with the risk of serosal involvement (P < .001). Both CT and surgery had an accuracy of 64% (P > .05) in predicting pathologic staging. CT overstaged only 4% of cases. CONCLUSIONS: Dynamic CT is a useful modality that can indicate inoperable disease, obviating the need for laparotomy in patients with gastric adenocarcinoma. CT can modify the surgical approach by suggesting unresectable or advanced disease. The low percentage of patients that are overstaged by CT, combined with its similar staging accuracy when compared with laparotomy, support its preoperative use in these patients.

Perry, A. R. and M. A. Shaw (2000). "Evaluation of functional outcomes (speech, swallowing and voice) in patients attending speech pathology after head and neck cancer treatment(s): development of a multi-centre database." J Laryngol Otol **114**(8): 605-15.

Since April 1997, in Melbourne, Australia, speech pathologists have collaborated to establish a prospective database of functional outcomes of speech, swallowing and voice for patients undergoing head and neck cancer treatments. Staff at eight acute care hospitals, all of which offer speech pathology for head and neck cancer services in Victoria, are contributing data, collated centrally, in an agreed pro forma. Early results are given (after 12 months' data collection). The implications for clinically-based research, and the future potential for benchmarking outcomes--by expansion of the rehabilitation database beyond the current participating sites--is discussed. This paper outlines the rationale of establishing the database is multicentered, and explores some of the complexities involved, including the challenges inherent in long-term accurate data collection in the head and neck cancer patient population. This work represents the development of an appropriate, usable tool for data collection on functional outcomes.

Perry, A. R., M. A. Shaw, et al. (2003). "An evaluation of functional outcomes (speech, swallowing) in patients attending speech pathology after head and neck cancer treatment(s): results and analysis at 12 months post-intervention." J Laryngol Otol **117**(5): 368-81.

We have earlier reported establishing a computerized database to audit functional outcomes in patients who underwent head and neck cancer treatment in Victoria, Australia and attended speech pathology services from April 1997-April 1999. This paper presents the statistical analyses and results from this study. Speech pathologists collected, prospectively, functional outcome data on 293 patients who underwent head and neck cancer treatment, and sent these for analysis to La Trobe University. Clinician and patient assessments of outcomes: speech, swallowing, activity, pain, employment, health, QOL status were made. Initial data on 293 patients were collected and data on mortality and morbidity were compiled at three, six and 12 months post-treatment. Within twelve months, 74 patients had died. Three, six and/or 12-month follow-up data was available on 219 patients, with both clinician and patient assessments of status completed. The status forms are presented as appendices to this paper. Complete status forms on 179 patients at 12 months were obtained. This clinical audit of functional outcomes represents the first study of this kind, collecting data from speech pathologists and patients in a multi-centre study of patients with head and neck cancer. We present data to demonstrate optimal recovery of function at six months, such that this may represent a good reference point for reporting and comparison of functional outcomes.

Pucar, D., H. Hricak, et al. (2007). "Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence." Int J Radiat Oncol Biol Phys **69**(1): 62-9.

PURPOSE: To determine whether prostate cancer local recurrence after radiation therapy (RT) occurs at the site of primary tumor by retrospectively comparing the tumor location on pre-RT and post-RT magnetic resonance imaging (MRI) and using step-section pathology after salvage radical prostatectomy (SRP) as the reference standard. METHODS AND MATERIALS: Nine patients with localized prostate cancer were treated with intensity modulated RT (69-86.4 Gy), and had pre-RT and post-RT prostate MRI, biopsy-proven local recurrence, and SRP. The location and volume of lesions on pre-RT and post-RT MRI were correlated with step-section pathology findings. Tumor foci >0.2 cm(3) and/or resulting in extraprostatic disease on pathology were considered clinically significant. RESULTS: All nine significant tumor foci (one in each patient; volume range, 0.22-8.63 cm(3)) were detected both on pre-RT and post-RT MRI and displayed strikingly similar appearances on pre-RT and post-RT MRI and step-section

pathology. Two clinically insignificant tumor foci (</=0.06 cm(3)) were not detected on imaging. The ratios between tumor volumes on pathology and on post-RT MRI ranged from 0.52 to 2.80. CONCLUSIONS: Our study provides a direct visual confirmation that clinically significant post-RT local recurrence occurs at the site of primary tumor. Our results are in agreement with reported clinical and pathologic results and support the current practice of boosting the radiation dose within the primary tumor using imaging guidance. They also suggest that monitoring of primary tumor with pre-RT and post-RT MRI could lead to early detection of local recurrence amenable to salvage treatment.

Qin, D. X., G. Q. Wang, et al. (1997). "Double blind randomized trial on occult blood bead (OBB) and gastroscopy-pathology screening for gastro-oesophageal cancer." Eur J Cancer Prev **6**(2): 158-61.

The study consists of two parts. In the first, 4,970 subjects were given the occult blood bead (OBB) test and 817 underwent gastroscopy: 40 of those screened were found to have cancer, 30 of which had early lesions (15 had carcinoma in situ). In the second part, a double blind randomized control study of the mass screening was conducted. All the tests were free of charge. Subjects over 30 years of age were persuaded to participate. Two-hundred and eight people accepted the OBB test, gastroscopy and histopathological assessment. A total of four cancers (two early, one moderate and one advanced) were detected by OBB test. If the OBB is carried out properly, gastro-oesophageal cancer is unlikely to be missed. We believe that OBB gastroscopy screening for oesophageal and gastric cancer is reliable and practical.

Qureshi, A., F. Bukhari, et al. (2009). "Spectrum of tamoxifen associated endometrial pathology in breast cancer patients." J Pak Med Assoc **59**(4): 249-50.

The objective of the study was to determine the incidence and type of endometrial abnormalities in long-term users of tamoxifen with breast cancer. All patients with a diagnosis of Oestrogen Receptor positive breast cancer on Tamoxifen therapy who had also undergone endometrial biopsy for abnormal bleeding or other symptoms were included. Among the 37 cases that had long-term follow up available, 21(57%) had evidence of endometrial pathology. There were seven cases of simple hyperplasia and thirteen of endometrial polyp. Only one case of endometrial carcinoma was seen. These findings support the association between prolonged tamoxifen therapy and endometrial pathology of possible neoplastic potential. Endometrial pathology is dependent on duration of exposure to Tamoxifen, therefore, close follow up of such patients is recommended.

Rabban, J. T. and D. A. Bell (2005). "Current issues in the pathology of ovarian cancer." J Reprod Med **50**(6): 467-74.

The majority of primary ovarian tumors are histologically classified as surface epithelial-stromal neoplasms. The malignant potential of such neoplasms may be categorized, on the basis of the extent of epithelial proliferation and stromal invasion, as benign, borderline or malignant. Recent efforts to further classify the malignant potential of such neoplasms have produced a new system for the histologic grading of ovarian carcinoma as well as new potential histologic predictors of behavior, including micropapillary morphology and stromal microinvasion in serous tumors. Among mucinous ovarian neoplasms, new criteria have been proposed to distinguish primary ovarian from metastatic carcinomas; the distinction may be difficult but has great clinical significance. The origin of ovarian mucinous tumors associated with pseudomyxoma peritonei has been reassessed. Finally, recent pathologic findings from prophylactic salpingo-oophorectomy specimens in patients with hereditary risks for ovarian carcinoma have highlighted the additional risk for fallopian tube carcinoma and primary peritoneal carcinoma. Special processing of the pathologic specimens is required to detect early and minimal neoplasia in this setting. These current issues in the pathology of ovarian carcinoma and their clinical significance form the basis of this review.

Raman, J. D., C. K. Ng, et al. (2005). "Bladder cancer after managing upper urinary tract transitional cell carcinoma: predictive factors and pathology." BJU Int **96**(7): 1031-5.

OBJECTIVE: To evaluate patients with a history of transitional cell carcinoma (TCC) of the upper urinary tract (UUT) to determine the incidence, pathological distribution, and risk factors for developing subsequent bladder tumours. PATIENTS AND METHODS: Between 1993 and 2003, 103 patients were treated at our institution for UUT-TCC. We reviewed demographic, clinical, surgical, and pathological data from these patients at a median follow-up of 38.7 months, and used univariate and multivariate analyses with logistic regression modelling to determine prognostic variables for bladder recurrences. RESULTS: In all, 51 (49.5%) patients developed bladder tumours after treatment for UUT-TCC, at a mean interval of 13.2 months. Patient age (P = 0.01), UUT tumour size (P = 0.03), UUT tumour multifocality (P = 0.05), a history of bladder tumours (P = 0.03), and the number of previous

bladder tumours (P = 0.05) predicted the development of bladder recurrences on univariate analysis. On multivariate analysis, only a previous history of bladder tumours (odds ratio 2.6, P = 0.05) remained significant. Over 90% of the recurrent bladder tumours were superficial, with two-thirds of these being low to moderate grade. Six patients had muscle-invasive disease, and five had a cystectomy. CONCLUSION: Bladder tumours occurred in half the patients after treatment for UUT-TCC; > 60% of these subsequent bladder tumours were superficial, low- to moderate-grade lesions. Neither the pathology of the UUT tumours nor the method of treatment for the UUT disease was associated with recurrent bladder tumours. Only a history of bladder cancer predicted the development of subsequent bladder tumours.

Recavarren-Arce, S., R. Leon-Barua, et al. (1991). "Helicobacter pylori and progressive gastric pathology that predisposes to gastric cancer." Scand J Gastroenterol Suppl **181**: 51-7.

Evidence is presented suggesting that infection by Helicobacter pylori triggers and continuously contributes to the pathophysiology of progressive gastric changes that can ultimately lead to gastric cancer. In Peru, especially in population groups of low socioeconomic status, infection by H. pylori begins earlier in life and is more prevalent and persistent than in developed countries. The infection produces a destructive lesion of the mucinous surface epithelium which probably enables other aggressive luminal factors to cause further mucosal damage. As a consequence, active chronic gastritis appears. The gastritis is of the superficial type at the beginning but may progressively change to atrophic. Chronic atrophic gastritis is found more frequently and at a younger age in dyspeptic patients with low socioeconomic status--that is, in patients having higher prevalence of persistent infection by H. pylori since earlier in life. When chronic atrophic gastritis becomes severe and extensive, hypochlorhydria ensues. Hypochlorhydria favors the appearance of bacterial overgrowth, nitrites, and N-nitroso compounds in the gastric lumen. N-nitroso compounds, because of their mutagenic-carcinogenic properties, probably induce gastric premalignant lesions like intestinal metaplasia and dysplasia of the gastric mucosa. Oral bismuth therapy apparently reverses H. pylori-associated gastric dysplasia. It is proposed that future programs designed for the control of gastric cancer would be incomplete if they do not include further evaluation of the many effects of infection by H. pylori on the gastric mucosa and of cost-effective methods to eradicate the infection.

Reuter, V. E. (2006). "The pathology of bladder cancer." Urology **67**(3 Suppl 1): 11-7; discussion 17-8.

Pathologists play an important role in the management of urinary bladder cancer by making a careful morphologic assessment of the primary tumor and its relation to adjacent structures. Ideally, evaluation of the primary site will segregate patients into groups with distinct clinical features, biologic behavior, and response to therapy. Traditionally, to accomplish this goal, pathologists have relied on factors such as histologic tumor type, grade, depth of invasion, and presence or absence of vascular invasion. Recently, in an effort to enhance our ability to subclassify these patients, we have introduced new modalities, such as flow cytometry, monoclonal antibodies, assessment of proliferative rate, and cytogenetics and molecular genetics. Without question we are advancing into an era in which tumors will be classified based on their molecular "fingerprint." Nevertheless, at this time, morphology remains the "gold standard" and, consequently, the best tool to assess the biologic potential of early bladder cancer. Despite this undeniable fact, there are many problems with the pathologic evaluation of these tumors, mostly because of the inherent subjectivity of the field and the lack of universal, standardized criteria for the evaluation of the above-mentioned morphologic parameters. Publications in peer-reviewed journals and the proliferation of educational opportunities by way of seminars, conferences, and web-based tutorials play an important role in keeping the practicing pathologist informed and up to date. As novel concepts and modern techniques are reported, their clinical value must be validated prospectively. Expert pathology review and establishment of exportable practice standards play an important role in the process.

Rohatgi, P. R., P. F. Mansfield, et al. (2006). "Surgical pathology stage by American Joint Commission on Cancer criteria predicts patient survival after preoperative chemoradiation for localized gastric carcinoma." Cancer **107**(7): 1475-82.

BACKGROUND: Preoperative chemoradiation for localized gastric cancer can modify baseline stage, as determined by surgical pathology stage. Therefore, the authors hypothesized that surgical pathology stage would be a better prognosticator of overall survival (OS) than baseline stage. METHODS: Patient populations were combined from 2 prospectively conducted, preoperative chemoradiation trials that used the same therapeutic strategy. Patients must have had localized gastric adenocarcinoma and were staged extensively, including endoscopic ultrasonography and

laparoscopy. Patients had to be fit for surgery medically with a technically resectable cancer. All patients provided written informed consent. Patients first received induction chemotherapy for up to 2 months followed by chemoradiation (45 grays) and an attempted surgery. OS was correlated with pretreatment and posttreatment parameters, including surgical pathology stage according to American Joint Commission on Cancer criteria. RESULTS: Of 74 patients who were registered, 69 patients (93%) had undergone surgery. Nineteen patients (26%) had a pathologic complete response (pathCR), and 55 patients (81%) had a curative (R0) resection. None of the pretreatment parameters correlated with OS; however, longer OS correlated with lower pathologic stage (P < .0001), R0 resection (P < .001), clinical response noted prior to surgery (P = .002), pathCR (P = .004), lower pathologic lymph node classification (P = .006), and lower pathologic tumor classification (P = .03). Pathologic stage and R0 resection were independent prognostic factors for OS (multivariate Cox model; both P = .05). CONCLUSIONS: When preoperative chemoradiation strategy was employed for gastric cancer, the surgical pathology stage, a reflection of cancer's biologic heterogeneity, was a better prognosticator of OS than the baseline clinical stage. Surgical pathology stage, in this setting, may serve as an intermediate endpoint for Phase II/III trials.

Rubin, M. A., T. A. Bismar, et al. (2004). "Prostate needle biopsy reporting: how are the surgical members of the Society of Urologic Oncology using pathology reports to guide treatment of prostate cancer patients?" Am J Surg Pathol **28**(7): 946-52.

Recent trends in prostate needle biopsy reporting have resulted in the inclusion of more information and new diagnostic categories. The goal of the current study was to survey surgical Members of the Society of Urologic Oncology to determine what information academic urologists consider important in the management of their prostate cancer (PCa) patients. A questionnaire was developed to investigate several areas of PCa biopsy reporting, which vary from institution to institution. Urologists were sent questionnaires and asked to return anonymous responses; 42 questionnaires were completely evaluated with a response rate of 76% (42 of 55). The urologists targeted for this survey were highly experienced with an average of 22 years in clinical practice (range, 6-35 years). On average, they performed 92 radical prostatectomies per year and 449 over the past 5 years (range, 60-1500) for a group total of 18,840 radical prostatectomies; 94% have their patient's biopsy reviewed prior to surgery. The primary and secondary Gleason pattern was required by 60% (25 of 42) of the respondents. In prostate needle biopsies containing only a single minute focus of PCa, only 41% (17 of 42) of respondents would request a Gleason score if not provided in the initial report. Interestingly, in biopsies with multiple positive cores from separate locations, 81% (34 of 42) use the highest Gleason score, regardless of the overall percentage involvement, to determine their treatment plan. Other pathology parameters requested by the respondents in descending order included: % involvement of the core by PCa (67%), the presence or absence of perineural invasion (38%), the number of cores with PCa (33%), and the length of core involvement (29%). Only 24% (10 of 42) of respondents use perineural invasion status to guide nerve-sparing surgery. The more radical prostatectomies performed by a surgeon, the greater the likelihood that they considered perineural invasion clinically important (Mann-Whitney, two-tailed, P = 0.015). The term atypical small acinar proliferation was uniformly considered sufficient to re-biopsy by 98% (41 of 42) of the urologists. This is the first study to survey urologists as to what information they require from prostate needle biopsy reports in their treatment planning of men with clinically localized PCa. With the exception of Gleason score, the use of detailed pathology information was variably used to guide treatment. PNI was not considered important by the majority of respondents. In contrast, atypical small acinar proliferation, a more recent diagnostic category, was recognized as important by nearly all respondents. Knowledge of how pathology biopsy reports are being used should help evaluate what data should be uniformly part of standard biopsy pathology report and help improve communication between pathologists and urologists.

Russo, J. and I. H. Russo (1992). "The pathology of breast cancer: staging and prognostic indicators." J Am Med Womens Assoc **47**(5): 181-7.

The natural history of breast cancer is complex and the treatment modalities need to be adjusted to this heterogeneous disease. Several prognostic indicators have been described for breast cancer, including the extent of axillary nodal metastasis, the size of the primary tumor mass, various histopathologic characteristics, estrogen and progesterone receptor content, tumor proliferation index, detection of oncogenes, tumor suppressor genes, loss of heterozygosity, and growth factors. Although no single parameter or combination of parameters can definitively predict the outcome of the disease, combined criteria such as tumor estrogen receptor content, cell proliferative index, and lymph node status are relevant for identifying subsets of breast cancer patients that may require different

therapeutic modalities. Detection of oncogenes, tumor suppressor genes, and growth factors need further evaluation to determine their usefulness as prognostic factors.

Ryden, L., M. Haglund, et al. (2009). "Reproducibility of human epidermal growth factor receptor 2 analysis in primary breast cancer: a national survey performed at pathology departments in Sweden." Acta Oncol **48**(6): 860-6.

BACKGROUND: HER2 is a treatment predictive factor for the effect of trastuzumab and associated with poor prognosis in breast cancer. The analysis of HER2 must be performed with good quality, with regard to both the immunohistochemical (IHC) and in situ hybridization (ISH) analysis. MATERIAL AND METHODS: A tissue microarray (TMA) including 11 breast cancer samples was sent twice (once in 2005 and again in 2006) to 24 pathology departments in Sweden. A questionnaire was also sent to the departments in 2006. RESULTS: With IHC, all departments reported the same results (0/1+ vs. 2+ vs. 3 + ) for three (2005) and six samples (2006). The mean kappa-value increased from 0.67 to 0.77, indicating a good reproducibility at both occasions. With fluorescence-ISH (FISH), the 11 departments using this technique reported the same results (amplified vs. normal) for nine (2005) and ten samples (2006). The mean kappa-value showed very good reproducibility both 2005 and 2006 (0.92 and 0.96, respectively). Based on the answers from the participating departments, the questionnaire revealed that 31% of primary breast cancer diagnosed in 2006 (n = 5 043) were 2 + /3+. FISH analysis of 2+ confirmed 12% of the samples to be amplified. The corresponding figure for 3 + was 90%. In total, 14.3% of the samples were HER2 positive (2+ and amplified, or 3 + ). DISCUSSION: The results obtained in this study indicate that the reproducibility for HER2 analysis is good (IHC) and very good (FISH) between the pathology departments in Sweden using TMA-based tumor samples. In 2006, 14.3% of invasive breast cancers were HER2 positive.

Sakamoto, G. and H. Sugano (1991). "Pathology of breast cancer: present and prospect in Japan." Breast Cancer Res Treat **18 Suppl 1**: S81-3.

Breast cancer among Japanese females is characterized by its relatively low incidence and better prognosis than among Caucasian females. The annual mortality due to breast cancer among Japanese is about one-fifth that among Caucasians. Comparison of case distribution by histological type indicates that the ratio of well-differentiated carcinoma is slightly higher among Japanese, while the ratio of poorly differentiated carcinoma is slightly higher among Caucasian females. It is noteworthy that the incidence of in situ and invasive lobular carcinoma among Japanese is much lower than among Caucasian females. The age distribution shows that breast cancer is more frequent among middle-aged females in Japan, but more common among aged females in the West. Breast cancer among Japanese females shows a better prognosis than among Caucasian females as a whole, even with equal tumor size and lymph node metastasis. As mentioned above, the morbidity and mortality rates of breast cancer among Japanese females are very low, but recently, both morbidity and mortality rates in Japan have been steeply increasing. For example, the mortality rate of breast cancer in Japan almost doubled during the past 20 years. Moreover, biological behavior of breast cancer among Japanese females has been recently changing. Time-trend data clearly indicate that breast cancer in Japan in the future will be much more like that in the West, and nowadays it is already westernizing.

Schwartz, A. M. and D. E. Henson (2007). "Diagnostic surgical pathology in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition)." Chest **132**(3 Suppl): 78S-93S.

OBJECTIVE: The objective of this study was to provide evidence-based background and recommendations for the development of American College of Chest Physicians guidelines for the diagnosis and management of lung cancer. METHODS: A systematic search of the medical and scientific literature using MEDLINE, MDCONSULT, UpToDate, Cochrane Library, NCCN guidelines, and NCI/NIH search engines was performed for the years 1990 to 2006 to identify evidence-based and consensus guidelines. The search was limited to literature on humans and articles in the English language. RESULTS: The pathologic assessment of lung cancers is based on a set of well-accepted findings, including histologic type, tumor size and location, involvement of visceral pleura, and extension to regional and distant lymph nodes and organs. Bronchial-based incipient neoplasia needs to be recognized both grossly and microscopically because these lesions may be multifocal and represent multistep carcinogenesis and may be amenable to therapy. Cytologic assessment of the individual with no symptoms is, as yet, of insufficient clinical benefit for screening of lung cancer. In challenging situations of pathologic differential diagnosis, additional studies may provide information that enables the separation of distinct tumor types. Pathobiological and molecular biological studies may yield prognostic and predictive information for clinical management and should be considered as part of protocol studies. Enhanced pathologic and molecular techniques may identify the

presence of micrometastatic disease within lymph nodes; however, the clinical utility of these approaches is still unresolved. Intraoperative consultations have high diagnostic accuracy and may aid ongoing treatment and management decisions. CONCLUSIONS: Pathologic assessment is a crucial component for the diagnosis, management, and prognosis of lung cancer. Selective diagnostic techniques and decision analysis will increase diagnostic accuracy. Cytologic screening, molecular characterization of tumors, and micrometastatic analysis are potential but not yet proved modalities for the evaluation of lung cancers.

Sezeur, A., F. P. Chatelet, et al. (2007). "Pathology underrates colon cancer extranodal and nodal metastases; ex vivo radioimmunodetection helps staging." Clin Cancer Res **13**(18 Pt 2): 5592s-5597s.

PURPOSE: Colorectal carcinoma is frequently accompanied by small lymph nodes metastases that often escape pathologic examination. We evaluated whether ex vivo radioimmunodetection with the Affinity Enhancement System (AES) could improve detection of mesocolonic metastases. EXPERIMENTAL DESIGN: A bivalent 111In-labeled hapten was injected (16 patients) 4 days after a bispecific antibody (anticarcinoembryonic antigen, antihapten). Surgery was done 1 to 3 days later, and radioactive uptake in the mesocolon was recorded. Extensive pathologic examination of the mesocolon (reference method) was done after fat dissolution. This method visualizes all lymph nodes but is not in routine use. RESULTS: The reference method disclosed 705 nodes. There was no significant difference between the number of node metastases detected by AES or by the reference method (16 versus 17). Better detection would have been obtained by AES than by routine pathology ($P<0.01$). In addition 12 extranodal metastases were found in this study of which eight were detected by AES. The prognostic importance of such extranodal metastases has been underlined in the literature. Routine pathology combined with AES would have disclosed all node metastases and 86% of total metastases versus 35% by routine pathology alone. CONCLUSIONS: Ex vivo radioimmunodetection could improve nodal and extranodal metastases detection in patients with colorectal cancer. Its value for improving pathologic analysis, together with the effect of these small metastases on prognosis, should be further evaluated. The benefit of adjuvant chemotherapy for patients upstaged with radioimmunodection should also be assessed because adjuvant chemotherapy improves the 5-year survival of stage III patients.

Shield, K., M. L. Ackland, et al. (2009). "Multicellular spheroids in ovarian cancer metastases: Biology and pathology." Gynecol Oncol **113**(1): 143-8.

Epithelial ovarian cancer (EOC) has a relatively high mortality rate ( approximately 55%). One of the presiding causes is that the current chemotherapeutic regimes are unable to achieve sustained remission, despite frequently producing a positive response at first treatment. One of the reasons that EOC is difficult to treat is that the mechanism of dissemination is unusual. EOC dissemination characteristically involves local invasion of pelvic and abdominal organs. Unlike many epithelial cancers, initial dissemination rarely requires the vasculature, although the vasculature is often implicated in the advanced stages of disease. Recently, it has become apparent that aggregates of malignant cells (spheroids) contained within malignant ascites represent a significant impediment to efficacious treatment of late stage EOC. In vivo, spheroids are present in the malignant ascites of EOC patients, while in vitro cultured spheroids are capable of tumorgenesis in vivo and display a reduced response to chemotherapeutic drugs when compared to monolayers. A major problem associated with the current generation of chemotherapy agents is that they do not address the anchorage- and vascular-independent growth conditions associated with a 3-dimensional structure that has formed and/or grown in suspension. Thus, spheroid formation may represent a key component of platinum/taxane-sensitive recurrence. If this is correct, a better understanding of spheroid biology may contribute to the identification of new treatment opportunities for the sustained treatment of metastatic EOC. This review article outlines the key biological features of spheroids, specifically discussing their role in EOC dissemination and chemo-response as well as providing insights into spheroid functionality.

Shyyan, R., S. Masood, et al. (2006). "Breast cancer in limited-resource countries: diagnosis and pathology." Breast J **12 Suppl 1**: S27-37.

In 2002 the Breast Health Global Initiative (BHGI) convened a panel of breast cancer experts and patient advocates to develop consensus recommendations for diagnosing breast cancer in countries with limited resources. The panel agreed on the need for a pathologic diagnosis, based on microscopic evaluation of tissue specimens, before initiating breast cancer treatment. The panel discussed options for pathologic diagnosis (fine-needle aspiration biopsy, core needle biopsy, and surgical biopsy) and concluded that the choice among these methods should be based on available tools and expertise. Correlation of pathology, clinical, and imaging findings was emphasized. A 2005 BHGI

panel reaffirmed these recommendations and additionally stratified diagnostic and pathology methods into four levels--basic, limited, enhanced, and maximal--from lowest to highest resources. The minimal requirements (basic level) include a history, clinical breast examination, tissue diagnosis, and medical record keeping. Fine-needle aspiration biopsy was recognized as the least expensive reliable method of tissue sampling, and the need for comparing its clinical usefulness with that of core needle biopsy in the limited-resource setting was emphasized. Increasing resources (limited level) may enable diagnostic breast imaging (ultrasound +/- mammography), use of tests to evaluate for metastases, limited image-guided sampling, and hormone receptor testing. With more resources (enhanced level), diagnostic mammography, bone scanning, and an onsite cytologist may be possible. Mass screening mammography is introduced at the maximal-resource level. At all levels, increasing breast cancer awareness, diagnosing breast cancer at an early stage, training individuals to perform and interpret breast biopsies, and collecting statistics about breast cancer, resources, and competing priorities may improve breast cancer outcomes in countries with limited resources. Expertise in pathology was reaffirmed to be a key requirement for ensuring reliable diagnostic findings. Several approaches were again proposed for improving breast pathology, including training pathologists, establishing pathology services in centralized facilities, and organizing international pathology services.

Silva, E., Z. Gatalica, et al. (2008). "Hereditary breast cancer: part II. Management of hereditary breast cancer: implications of molecular genetics and pathology." Breast J **14**(1): 14-24.

Management of patients at high risk for hereditary breast cancer (HBC) must critically assess its phenotypic and genotypic heterogeneity, particularly evidenced by the varying spectra of cancer sites that are integral to the respective HBC syndromes. Targeted management must consider their biology, pathology, and molecular genetics, all in concert with their respective carcinogenic pathways, as they may differ significantly from one breast cancer syndrome to the next. A striking example of management differences pertains to BRCA1 and BRCA2 mutation-positive breast cancers wherein those with BRCA1 mutations are frequently estrogen receptor (ER)-negative in contrast to BRCA2 mutations which are more frequently ER-positive; therein, significant differences exist with respect to anti-estrogen therapy which will be more amenable to BRCA2 versus BRCA1 mutation carriers manifesting breast cancer. In turn, tumors that are negative for ER, PR, and Her2-neu, often referred to as "triple negative" tumors, may also harbor a unique basal-like gene expression profile and are characterized by poor prognosis wherein endocrine and/or Her2-neu-targeted therapies are not effective treatment options. A further confounder pertains to the lifetime risk for ovarian cancer, which differs strikingly between BRCA1 mutation carriers, who show a 40-60% lifetime risk, and their BRCA2 counterparts, who carry a lifetime risk of approximately 12-15% for ovarian cancer. It is clear that as we learn more about the biology and the molecular aspects of hereditary forms of breast cancer, it will be compelling for the clinician to integrate this knowledge with pharmacologic, radiologic, and surgical treatment options for these high-risk patients.

Simpson, J. F. and D. L. Page (1996). "The role of pathology in premalignancy and as a guide for treatment and prognosis in breast cancer." Semin Oncol **23**(4): 428-35.

This review emphasizes tissue pathology and its practical relevance to patient management in premalignant breast disease and established breast cancer. The rationale and criteria for recognizing benign lesions that indicate a subsequent increased risk for cancer development are now well established, having been confirmed in several large epidemiologic studies. Our understanding of the heterogeneous nature of ductal carcinoma in situ (DCIS) continues to evolve. Recent efforts to classify DCIS into clinically meaningful categories underscore the central role of histopathology in the management of this disease. Through long term follow up studies, small examples of noncomedo DCIS treated by biopsy alone may predict local recurrence. Adequate surgical excision, however, avoids this possibility in the predominance of such cases. For invasive carcinomas, prognostic issues extend beyond predicting survival after local treatment. Now that the efficacy of systemic chemotherapy is established, the question is whether this therapy will be of use to a particular patient or group of similar patients. The list of possible clinically useful subcategories of prediction is growing and under active development. Prognostic factors that are in general use, having been repeatedly validated, particularly stage and histologic grade, as well as those that are emerging but in need of validation, are reviewed.

Simpson, J. F. and D. L. Page (1997). "Pathology of preinvasive and excellent-prognosis breast cancer." Curr Opin Oncol **9**(6): 512-9.

Our review of recent developments in breast cancer involving evaluation of cellular and tissue samples is targeted at indicators of elevated risk of sufficient magnitude to attain clinical significance;

lesions unassociated with metastatic capacity but of sufficient risk to attain that capacity that formal treatment is necessary, ie, ductal carcinoma in situ; and indicators of good prognosis in invasive cancer. Ductal carcinoma in situ has been the subject of much recent discussion. We highlight particularly the area of stratification or classification within this group of lesions. The importance of the extensiveness of ductal carcinoma in situ in the prediction of local recurrence within the conserved breast is included. Also discussed are advances in diagnostic techniques, specifically core needle biopsies performed under mammographic and ultrasonographic guidance.

Simpson, J. F. and D. L. Page (1999). "Pathology of preinvasive and excellent-prognosis breast cancer." Curr Opin Oncol **11**(6): 442-6.

Evaluation of tissue and cellular samples for diagnosis, risk assessment, and prognosis in breast cancer is the subject of this review. We emphasize indicators of elevated risk for breast cancer and carcinomas in situ and indicators of good prognosis in invasive breast cancer. The importance of ductal carcinoma in situ to considerations in breast conservation and prevention is highlighted. Special types of breast cancer, immunohistochemistry, histologic grading, and the relevance of core biopsy to diagnostic certainty are considered. We also add a brief note about the escalating role of nodal micrometastases and sentinel node biopsy in the definition of minimal regional disease.

Simpson, J. F. and D. L. Page (2001). "Pathology of preinvasive and excellent prognosis breast cancer." Curr Opin Oncol **13**(6): 426-30.

We review recent reports on breast cancer and its predictors, emphasizing the clinical utility of tissue samples from patients. We highlight indicators of increased cancer risk and lesions without metastatic capacity at time of detection, but of sufficient risk of attaining metastatic capacity that treatment is mandated ( ie, ductal carcinoma in situ ). Emphasized are histologic features of importance in stratification of ductal carcinoma in situ. We also review invasive lesions with little capacity for metastatic behavior and indicators of low malignant potential. Included are several papers reviewing the usefulness of histologic grading, emphasizing mitotic counts. Also, the continuing utility of recognizing some special and unusual types of breast cancer is detailed. Sentinel lymph node evaluation by histology is included because some minimal or artifactual findings in lymph nodes can mimic true metastases.

Slootweg, P. J., G. J. Hordijk, et al. (2002). "Treatment failure and margin status in head and neck cancer. A critical view on the potential value of molecular pathology." Oral Oncol **38**(5): 500-3.

Molecular pathology may demonstrate tumour cells not detected by histology. The idea has emerged that these cells influence the prognosis negatively and that their detection will lead to more appropriate treatment and improved patient survival. We theorized that tumour cells at surgical margins overlooked by the pathologist should demonstrate their clinical significance by causing recurrences at the primary site in the patients reported to have tumour-free margins by histology. To assess this assumption, we investigated the prognostic influence of the histologically determined status of the surgical margins. The material that formed the basis of this study consisted of 394 patients that underwent resection for their primary tumour during the years 1990-1995. In 207 patients, initial treatment was complete as assessed by conventional histopathological examination of the surgical specimen. In 187 patients, initial treatment was incomplete, defined as tumour in or close to the margin, or mild, moderate or severe dysplasia or in situ cancer at the margin. Causes for treatment failure were recorded for both groups separately. In the group with tumour-free margins, 16.9% had a second primary head and neck cancer, 8.2% had a second tumour in the lung, 10.6% had recurrent disease in the neck, 2.9% had distant metastasis, and 3.9% had local recurrence at the same site as the primary cancer. For the group without tumour-free margins, these figures were the following: second primary in the head and neck area: 17.1%, second primary in the lung: 7.0%, recurrent disease in the neck: 11.8%, distant metastasis: 8.0% and local recurrence at the primary site: 21.9%. Local recurrences were rare in patients in which the pathologist reported the resection to be complete. Although there may be tumour cells in surgical margins that evade histological detection, their clinical impact appears to be almost negligible.

Smouse, J. H., E. S. Cibas, et al. (2009). "EGFR mutations are detected comparably in cytologic and surgical pathology specimens of nonsmall cell lung cancer." Cancer **117**(1): 67-72.

BACKGROUND: Somatic mutations in the epidermal growth factor receptor (EGFR) are present in approximately 10% of nonsmall cell lung cancers, and higher in never-smokers, women, and Asians. Small in-frame deletions in exon 19 ( approximately 45%) and L858R mutation in exon 21 ( approximately 40%) predict response to treatment with tyrosine kinase inhibitors, whereas some others herald resistance. Direct sequencing of tumor DNA detects all EGFR mutations, but is limited by interference from nonmalignant cells within the samples. Concern

over such interference has discouraged testing cytologic samples, but the adequacy of cytologic specimens for EGFR sequencing has not been studied. METHODS: EGFR sequencing of surgical and cytologic specimens at Brigham and Women's Hospital over the past 2 years was reviewed. Of 239 specimens, 227 (95%) were surgical, and 12 (5%) were cytologic (fine needle aspirations, pleural fluids, bronchial washings, and bronchoalveolar lavages). RESULTS: Sixty-three (28%) surgical specimens showed EGFR mutations, whereas 143 (63%) were negative, 8 (3.5%) failed, and 14 (6.2%) were inconclusive (negative result in a heterogeneous sample). Seven (58%) cytologic specimens showed EGFR mutations, whereas 4 (33%) were negative, and 1 (8.3%) was inconclusive. Cytologic specimens were more likely to have a mutation than surgical specimens (P = .02). There was no significant difference in the frequency of inconclusive results. CONCLUSIONS: Cytologic specimens are suitable for EGFR sequencing and show comparable sensitivity for mutation detection as compared with surgical specimens. The suitability of a sample should be determined on a case-by-case basis, and cytologic samples should not be dismissed as inadequate without a thorough review.

Snozek, C. L., D. J. O'Kane, et al. (2009). "Pharmacogenetics of solid tumors: directed therapy in breast, lung, and colorectal cancer: a paper from the 2008 william beaumont hospital symposium on molecular pathology." J Mol Diagn **11**(5): 381-9.

Genetic variability in drug-metabolizing enzymes and signaling pathways affects chemotherapy-related toxicity and treatment outcome in cancer. In breast and colorectal cancer, polymorphisms in metabolic enzymes involved in tamoxifen and irinotecan therapies has led the U.S. Food and Drug Administration to address genetic factors relevant to patient consideration of treatment with these compounds. Tamoxifen therapeutic failure in breast cancer has been associated with reduced CYP2D6 activity due to inefficient activation of tamoxifen. Irinotecan toxicity in colorectal cancer is more common in patients with reduced-activity UGT1A alleles, resulting in excessive exposure to the potent SN-38 metabolite. In colorectal and lung cancers, somatic mutations in the epidermal growth factor receptor and downstream signaling molecules have been associated with the therapeutic outcome of epidermal growth factor receptor-directed therapies. This review discusses the current knowledge regarding the utility of single gene-UGT1A1, CYP2D6, EGFR, and KRAS-or multigene analysis, for optimizing breast, colorectal, and lung cancer therapy. Current advances in these areas highlight how pharmacogenetics help personalized decision-making for patient management.

Solin, L. J., B. L. Fowble, et al. (1991). "The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer." Int J Radiat Oncol Biol Phys **21**(2): 279-87.

To evaluate the significance of the pathology margins of the tumor excision on the outcome of treatment, an analysis was performed of 697 consecutive women with clinical Stage I or II invasive carcinoma of the breast treated with breast-conserving surgery and definitive irradiation. Complete gross excision of the primary tumor was performed in all cases, and an axillary staging procedure was performed to determine pathologic axillary lymph node status. The 697 patients were divided into four groups based on the final pathology margin from the primary tumor excision or from the re-excision if performed. These four groups were: (a) 257 patients with a negative margin (greater than 2 mm), (b) 57 patients with a positive margin, (c) 37 patients with a close margin (less than or equal to 2 mm), and (d) 346 patients with an unknown margin. The patients with positive final pathology margins were focally positive on microscopic examination. Patients with grossly positive margins or with diffusely positive microscopic margins were treated with conversion to mastectomy. There was a significant difference in the total radiation dose for the four groups (median dose of 6000 vs 6500 vs 6400 vs 6240 cGy, respectively; p less than .0001). There was no significant difference among the four groups for 5-year actuarial overall survival (p = .19), no evidence of disease (NED) survival (p = .95), or relapse-free survival (p = .80). There was no significant difference among the four groups for five year actuarial local or regional control (all p greater than or equal to .29). Subset analyses did not identify any poor outcome subgroups. These results have demonstrated that selected patients with focally positive or close microscopic pathology margins can be adequately treated with definitive breast irradiation. Patient selection and the technical delivery of radiation treatment including a boost may have been important contributing factors to the good outcome in these patients.

Staradub, V. L., K. A. Messenger, et al. (2002). "Changes in breast cancer therapy because of pathology second opinions." Ann Surg Oncol **9**(10): 982-7.

BACKGROUND: Examination of pathology slides is a routine part of a breast cancer second opinion. The purpose of this study was to determine how often the pathologic second opinion (1) altered

the diagnosis and (2) resulted in a change in the surgical procedure. METHODS: Patients presenting between 1997 and 2001 for a second opinion after a biopsy diagnosis of breast cancer (invasive or noninvasive) were included in this study. RESULTS: There were 340 patients presenting for second opinions regarding 346 breast cancers. Sixty-eight pathologic second opinions (20%) did not result in any change in pathology or prognostic factors, whereas in the remaining 80%, some change occurred. Major changes that altered surgical therapy occurred in 7.8% of cases, and pathology review provided additional prognostic information in 40%. Changes were more common in in situ carcinoma than invasive carcinoma (P =.004), but biopsy type (core vs. excisional biopsy) was not a significant predictor of change in pathologic information. CONCLUSIONS: This study confirms the benefit of a pathology second opinion to improve preoperative estimates of prognosis and to determine the appropriate surgical procedure. Missing information on grade and histological subtype was responsible for a large number of cases, suggesting a need for widespread application of standardization and quality improvement in pathology reporting.

Stemmermann, G. N. and C. Fenoglio-Preiser (2002). "Gastric carcinoma distal to the cardia: a review of the epidemiological pathology of the precusors to a preventable cancer." Pathology **34**(6): 494-503.

A distinctive gastritis precedes the development of cancer distal to the cardia. Helicobacter pylori infection and the use of pickled foods as substitutes for fresh fruits and vegetables constitute the most important environmental factors that generate this gastritis. This review describes the anatomical changes that characterise the step-by-step evolution of a process that begins in childhood and culminates in invasive cancer in middle and old age. Progression of the gastritis can be followed by measuring the host antibody response to the H. pylori infection and by serum assays that indicate loss of parietal cell mass. Cancer of the distal stomach will disappear if adequate, sanitary housing and year-round fresh vegetables are made available to all economic levels of society. Programmes that offer these reforms must be sustained over several generations, since the anatomical changes that precede gastric cancer are probably not reversible and begin early in life. In the absence of these reforms, death from gastric cancer may be prevented if patients with asymptomatic, early cancers are identified. High H. pylori antibody levels and serum pepsinogen assays may be used to identify persons with the extensive gastritis that favours the presence of such early cancers.

Suekane, S., M. Noguchi, et al. (2007). "Percentages of positive cores, cancer length and Gleason grade 4/5 cancer in systematic sextant biopsy are all predictive of adverse pathology and biochemical failure after radical prostatectomy." Int J Urol **14**(8): 713-8.

AIM: We investigated whether the quantitative parameters of systematic sextant biopsies were predictive of either adverse pathological findings or disease recurrence after radical prostatectomy (RP). METHODS: We retrospectively evaluated a total of 117 men with untreated prostate cancer whose needle biopsies were matched with RP specimens. The pretreatment parameters of the serum prostate-specific antigen (PSA), the PSA density, the percentage of positive biopsy cores, the percentage of cancer length and the percentage of Gleason grade 4/5 cancer in the biopsy were determined and compared with the pathological features of prostate cancer in RP specimens. These pretreatment parameters and pathological factors in the RP specimens, including the cancer volume, the percentage of Gleason grade 4/5 cancer, the positive surgical margin and the seminal vesicle invasion were evaluated for their ability to predict the disease recurrence. RESULTS: The percentages of positive biopsy cores, the Gleason grade 4/5 cancer in the biopsy and the cancer length in the biopsy had a weak correlation with the cancer volume in RP specimens (r = 0.373, 0.345, 0.408, respectively). All quantitative biopsy parameters were strongly predictive of the non-organ-confined status, the positive surgical margin and the seminal vesicle invasion in the logistic regression analysis. The percentage of positive biopsy cores and the percentage of Gleason grade 4/5 cancer in the biopsy predicted biochemical failure after RP. CONCLUSION: These results indicate that quantitative biopsy parameters are independent predictors of the adverse pathology of prostate cancers and disease recurrence after RP.

Tachezy, R., P. Davies, et al. (2008). "Consensus recommendations for cervical cancer prevention in the Czech Republic: a report of the International Conference on Human Papillomavirus in Human Pathology (Prague, 1-3 May 2008)." J Med Screen **15**(4): 207-10.

A comparison of cervical cancer incidence and mortality in the Czech Republic with that from other countries shows that the burden of cervical cancer here is considerably higher than in Western Europe, where screening is widespread. In May 2008, the International Conference on Human Papillomavirus in Human Pathology was convened to review the latest evidence and to formulate consensus recommendations for the reduction of cervical cancer rates. The Czech Republic is spending considerable resources on cervical cancer prevention, but these

resources are being used inefficiently. The current system is characterized by a lack of coordination and monitoring that leads to the over-screening of a minority of women while the majority of the target population are under-screened or not screened at all. It was recommended that a comprehensive, organized programme be implemented, coordinated by an independent administrative body with legal and budgetary responsibility. As the laboratory infrastructure and professional technical skills required for a quality-assured organized screening programme are already in place, implementation of this programme would not require much in the way of additional resources to produce substantial cost-effective reductions in cervical cancer rates.

Torkzad, M., J. Lindholm, et al. (2003). "Retrospective measurement of different size parameters of non-radiated rectal cancer on MR images and pathology slides and their comparison." Eur Radiol **13**(10): 2271-7.

There are no non-invasive methods to assess the real tumor size in rectal cancer prior to surgery, especially following radio/chemotherapy. Magnetic resonance imaging is gaining increasing acceptance as the primary modality at many centers for evaluation of pelvic malignancies including rectal cancers. The aim of this study was to evaluate if the tumor size as assessed by stereological or metric means on MRI correlates to the corresponding pathologic findings. To our knowledge, no such previous work has been reported in the literature. From the Cancer Register Center, 18 patients in the age range of 39-90 years with rectal cancer who had complete preoperative MR with subsequent giant section pathological examinations of the resected bowel were included. The tumor size was measured on MR and histopathologic specimen using both a stereologic and a metric mode. The measured parameters included the maximum transverse area occupied by the tumor, thickness, width, and the length of tumor and the volume of the tumor measured in two different fashions by the product of area and length (al) or the product of thickness, width, and length (twl). The depth of tumor infiltration (T) and presence of local lymph node metastases (N) were also separately evaluated on the histopathologic specimen. There were 1, 4, 12, and 1 patients with tumor stages T1, T2, T3, and T4, respectively. The mean thickness, width, length, area, and volumes, al and twl, were 1.62, 2.8, and 4.78 cm, and 4.72 cm2, 26.29 cm3, and 20.07 cm3, respectively. Regression curves were drawn for above-mentioned parameters. They showed some correlation with square correlation coefficient measuring between 0.38 and 0.82. The best correlation was seen for area (0.75) and volume measured by the product of area and length of the tumor (0.82). With the formula proposed from this material, we assume that rectal tumors can be measured on MR images using a metric model, especially area and the volume (the product of area and length), and then extrapolated to what we would expect from pathology, hence providing us with a tool where we could measure tumor response after neoadjuvant therapy.

Tsou, Y. A., J. H. Hua, et al. (2006). "Analysis of prognostic factors of chemoradiation therapy for advanced hypopharyngeal cancer--does tumor volume correlate with central necrosis and tumor pathology?" ORL J Otorhinolaryngol Relat Spec **68**(4): 206-12.

OBJECTIVES: Not all patients with hypopharyngeal cancer who undergo concurrent chemoradiation therapy have a good prognosis. We hope to find the significant prognostic factors that could help us in patient selection for concurrent chemoradiation therapy. STUDY DESIGN: We used a retrospective analysis on several prognostic factors which may affect the treatment outcome and prognosis. METHODS: We studied 51 patients with stage III-IV hypopharyngeal cancer who underwent chemoradiation therapy as the first treatment method. Possible significant prognostic factors (i.e. tumor volume, central necrosis, pathology, age) were collected to determine whether they correlate with local disease control and survival. RESULTS: Primary tumor volume correlated with local disease control and survival. The greatest risk for local failure was found among patients with primary tumor volumes >19.0 ml ($p = 0.001$). Other relatively significant prognostic factors were pathology and central necrosis. The survival rate among patients with primary tumor volumes >19.0 ml was only 39.3% compared with 78.3% for patients with volumes <19.0 ml ($p = 0.036$). A proportional hazard model indicated that significant parameters associated with overall survival were primary tumor volume ($p = 0.036$) and central necrosis ($p = 0.008$). According to the cancer cell differentiation, the hazard risk in the well-differentiated group was 5.62 folds higher than in the poorly differentiated group ($p = 0.05$). Patients with an initial complete response had a primary tumor volume <19 ml ($p = 0.001$, 0.016), poorly differentiated pathology ($p = 0.001$, 0.016), and no central necrosis ($p = 0.001$, 0.016). Other relatively poor significant factors were T stage above III ($p = 0.047$), cervical lymphadenopathy beyond level II ($p = 0.046$), and a nodal volume >10.0 ml ($p = 0.029$). N stage, age and gender were not significant prognostic factors. CONCLUSION: Tumor volume is the most important prognostic factor of treatment outcome for patients with hypopharyngeal cancer and should always be taken into consideration in treatment planning. Other

possible prognostic factors which affect the initial complete response rate and survival rate including central necrosis, pathology, nodal number and nodal volume, T stage above III, and cervical lymphadenopathy beyond level II have a relatively low correlation with treatment outcome. In our study, there was a correlation between tumor volume and central necrosis, but no significant correlation between pathological differentiation and tumor volume, although both affect treatment outcome.

Tsuda, H., F. Akiyama, et al. (1998). "Establishment of histological criteria for high-risk node-negative breast carcinoma for a multi-institutional randomized clinical trial of adjuvant therapy. Japan National Surgical Adjuvant Study of Breast Cancer (NSAS-BC) Pathology Section." Jpn J Clin Oncol **28**(8): 486-91.

BACKGROUND: A multi-institutional randomized clinical trial of adjuvant therapy for patients with high-risk node-negative (n0) breast cancer has been undertaken in Japan. The pathology panel was organized in order to establish histological criteria to identify patient groups with higher rates of recurrence. METHODS: Initially, three pathologists independently judged the nuclear grade, composed of nuclear atypia and mitotic counts, of 100 n0 invasive ductal carcinomas, focusing on interobserver variation of the nuclear grade and its correlation with patient prognosis. These pathologists then gave consensus histological types and nuclear grades for 130 other n0 breast carcinomas and examined the prognostic significance of the grade. RESULTS: In the first study, nuclear grade 2-3 significantly identified a patient group with a rate of recurrence of 17-20% by any pathologists and the degree of agreement for the grade was fair. In the second study, the consensus type and nuclear grade identified a group (n = 66) with a 22% recurrence rate and another group (n = 64) with a 3.6% recurrence rate at 10 years. In 12 tumors, the resection-fixation interval of the tumor did not generate any significant difference in mitotic counts. CONCLUSIONS: The histological type and the nuclear grade clearly identified a higher-risk patient group with n0 breast carcinoma, and may be applied to the multi-institutional protocol study when the criteria have been well standardized by the pathologists.

Van Der Meijden, A., R. Sylvester, et al. (2000). "The role and impact of pathology review on stage and grade assessment of stages Ta and T1 bladder tumors: a combined analysis of 5 European Organization for Research and Treatment of Cancer Trials." J Urol **164**(5): 1533-7.

PURPOSE: Pathological interpretations are largely subject to interpathologist and intrapathologist variation. Differences in tumor stage and grade exist in local and review pathological findings in patients with stage Ta-T1 bladder tumors who are entered in randomized trials of adjuvant treatment after transurethral resection. Because they are diagnosed and treated based on local pathological results, it is important to determine the reliability of local pathological evaluations and the extent to which pathology review may change the treatment decision process. MATERIALS AND METHODS: We assessed local and review pathology results in 1,400 patients treated in 5 European Organization for Research and Treatment of Cancer randomized phase III trials comparing various adjuvant prophylactic treatment strategies for primary or recurrent stage Ta-T1 transitional cell bladder cancer. RESULTS: We noted large variations in T category and grade. Pathology review down staged T category to stage Ta in 53% of cases originally classified as stage T1. There was agreement in only 57% and 50% of stage Ta grade 1 and stage T1 grade 3 cases, of which 10% were reclassified as muscle invasive disease greater than stage T1. While T category and grade have prognostic importance, differences in the prognosis based on local and review pathological studies were slight. CONCLUSIONS: Pathology review is not mandatory in low and intermediate risk cases since it has little impact on the prognosis and treatment decision making. In high risk cases of stage T1 grade 3 disease stage or grade is often changed, so that review remains essential in this subgroup.

Van Gogh, C. D., H. F. Mahieu, et al. (2007). "Voice in early glottic cancer compared to benign voice pathology." Eur Arch Otorhinolaryngol **264**(9): 1033-8.

The purpose of this study is to compare (Dutch) Voice Handicap Index (VHIvumc) scores from a selected group of patients with voice problems after treatment for early glottic cancer with patients with benign voice disorders and subjects from the normal population. The study included a group of 35 patients with voice problems after treatment for early glottic cancer and a group of 197 patients with benign voice disorders. Furthermore, VHI scores were collected from 123 subjects randomly chosen from the normal population. VHI reliability was high with high internal consistency and test-retest stability. VHI scores of glottic cancer patients were similar to those of patients with voice problems due to benign lesions. Both groups of patients were clearly deviant from the normal population. Within the normal population, 16% appeared to have not-normal voices. Based on ROC curves a cut-off score of 15 points was defined

to identify patients with voice problems in daily life. A clinical relevant difference score of 10 points was defined to be used for individual patients and of 15 points to be used in study designs with groups. Patients with voice problems after treatment for early glottic cancer encounter the same amount of problems in daily life as the other voice-impaired patients. The VHI proved to be an adequate tool for baseline and effectiveness measurement of voice.

Veltri, R. W., M. A. Khan, et al. (2004). "Ability to predict metastasis based on pathology findings and alterations in nuclear structure of normal-appearing and cancer peripheral zone epithelium in the prostate." Clin Cancer Res **10**(10): 3465-73.

PURPOSE: Malignant transformation in the prostate produces significant alterations in glandular architecture (Gleason grade) and nuclear structure that provide valuable prognostic information. Normal-appearing nuclei (NN) adjacent to cancer may also have altered functions in response to malignancy. We studied NN adjacent to peripheral zone (PZ) prostate cancer (PCa), as well as the PZ cancer nuclei (CaN) using quantitative image cytometry. The nuclear structure information was combined with routine pathological findings to predict metastatic PCa progression and/or death. EXPERIMENTAL DESIGN: Tissue microarrays of normal-appearing and cancer areas were prepared from 182 pathologist-selected paraffin blocks. Feulgen-stained CaN and NN were captured from the tissue microarrays using the AutoCyte Pathology Workstation. Multivariate logistic regression was used to calculate quantitative nuclear grade (QNG) solutions based on nuclear morphometric descriptors determined from NN and CaN. Multivariate logistic regression and Kaplan-Meier plots were also used to predict risk for distant metastasis and/or PCa-specific death using QNG solutions and routine pathology. RESULTS: The pathology model yielded an area under the receiver operator characteristic curve of 72.5%. The QNG-NN and QNG-CaN solutions yielded an area under the receiver operator characteristic curve of 81.6 and 79.9%, respectively, but used different sets of nuclear morphometric descriptors. Kaplan-Meier plots for the pathology variables, the QNG-NN and QNG-CaN solutions, were combined with pathology to defined three statistically significantly distinct risk groups for distant metastasis and/or death ($P < 0.0001$). CONCLUSIONS: Alterations in cancer or normal-appearing nuclei adjacent to peripheral zone cancer areas can predict PCa progression and/or death. The QNG-NN and QNG-CA solutions could be combined with pathology variables to improve the prediction of distant metastasis.

Walker, R. A., J. L. Jones, et al. (1997). "Molecular pathology of breast cancer and its application to clinical management." Cancer Metastasis Rev **16**(1-2): 5-27.

Breast cancer is a major cause of morbidity and mortality in women in many parts of the world. Breast carcinomas are heterogenous in their biological and clinical behaviour and a greater understanding of how they develop and progress could lead to more directed forms of screening and therapy. It is important to determine the molecular mechanisms underlying the natural history of breast cancer. Developments in the techniques for molecular analysis have meant that they can now be applied to a large range of clinical material such as cytological preparations and fixed, embedded material, so increasing the potential for relating any molecular alterations to clinical behaviour and response to therapy. In this review we consider recent developments in three areas of importance to breast cancer; genetic analysis-oncogenes, tumour suppressor genes, loss of heterozygosity, microsatellite instability, familial breast cancer; steroid receptors, oestrogen regulated proteins, epidermal growth factor receptor, growth factors particularly transforming growth factor beta; and cell adhesion, invasion and metastasis-E-cadherin, integrins, proteases. These are discussed in relation to potential for screening, prognosis and treatment.

Walker, R. A. and J. M. Varley (1993). "The molecular pathology of human breast cancer." Cancer Surv **16**: 31-57.

Perhaps one of the most exciting recent developments in breast cancer research is the steadily increasing number of small screen detected lesions which are available for study. These samples will allow a number of questions of key importance to the development and progression of breast cancer to be answered. For example, the relationship between a variety of benign and premalignant lesions and frankly invasive breast carcinomas can be examined to determine the sequence of progression, if indeed such a sequence exists. Subtypes of screen detected lesions may be identified in which different genetic events have occurred, and the relationship between these genetic events and progression may be established. Such studies could identify groups of women for whom no further treatment is required or those for whom adjuvant therapy, radiotherapy or further surgery is indicated. A number of genetic alterations have now been identified that seem to be independent indicators of prognosis. Such alterations include overexpression of c-erbB2 and mutation of TP53. Although there is still some debate about the statistical significance of data from a number of different

groups, it seems certain that the status of a number of genes will provide prognostic information to augment existing criteria. There is an urgent need for an examination of a large panel of breast tumours for a number of key genetic alterations and for a critical evaluation of all the changes to existing clinical variables such as clinical stage, grade, survival and relapse times and growth factor receptors. Molecular pathology is providing new and exciting insights into the pathogenesis of human breast cancer, and molecular events associated with inherited breast disease, early stages, progression and metastasis of breast cancer are now becoming better understood.

West, N. P., E. J. Morris, et al. (2008). "Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study." Lancet Oncol **9**(9): 857-65.

BACKGROUND: High-quality rectal cancer surgery is known to improve patient outcome. We aimed to assess the quality of colon cancer surgery by studying the extent of variation in the plane of surgical resection, the amount of tissue removed, and its association with survival. METHODS: All resections for primary colon adenocarcinoma done at Leeds General Infirmary (Leeds, UK) between Jan 1, 1997, and June 30, 2002, were identified. The specimens were photographed and graded according to the plane of mesocolic dissection. Tissue morphometry was done on 253 tumours. Univariate and multivariate models were used to ascertain whether there was an association with 5-year survival. The primary outcome measure was overall survival defined as death from any cause. FINDINGS: 521 cancers were identified, 122 were excluded because of either no photographic images or insufficient images to allow retrospective grading, leaving 399 specimens for analysis. There was marked variation in the proportion of each plane of surgery: muscularis propria in 95 of 399 (24%) specimens, intramesocolic in 177 of 399 (44%) specimens, and mesocolic in 127 of 399 (32%) specimens. Mean cross-sectional tissue area outside the muscularis propria was significantly higher with mesocolic plane surgery (mean 2181 [SD 895] mm(2)) compared with intramesocolic (mean 2109 [1273] mm(2)) and muscularis propria plane (mean 1447 [913] mm(2)) surgery (p=0.0003). There was also a significant increase in the distance from the muscularis propria to the mesocolic resection margin with mesocolic plane surgery (mean 44 [21] mm) compared with intramesocolic (mean 30 [16] mm) and muscularis propria plane (mean 21 [12] mm) surgery, which was independent of tumour site (all excisions p<0.0001). We noted a 15% (95% CI) overall survival advantage at 5 years with mesocolic plane surgery compared with surgery in the muscularis propria plane (HR 0.57 [0.38-0.85], p=0.006) in univariate analysis. However, this association was no longer significant in the multivariate model (HR 0.86 [95% CI 0.56-1.31], p=0.472), but was especially noted in patients with stage III cancers (HR 0.45 [95% CI 0.24-0.85], p=0.014; multivariate analysis). The plane of surgery and amount of mesocolon removed varied between the different sites with better planes in left-sided resections than right-sided ones, which were better than transverse resection (p<0.0001). INTERPRETATION: As previously shown in the rectum, we have now shown there is marked variability in the plane of surgery achieved in colon cancer. Improving the plane of dissection might improve survival, especially in patients with stage III disease. If confirmed by clinical trial data, such as from the ongoing National Cancer Research Institute Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy for colon cancer (FOxTROT) trial of neoadjuvant chemotherapy in advanced resectable colon cancer, improvement of the plane of dissection might be a new cost-effective method of decreasing morbidity and mortality in patients with colon cancer.

Wijetunga, L. H., H. L. Carmalt, et al. (1996). "A review of pathology reporting for breast cancer." Aust N Z J Surg **66**(11): 723-6.

BACKGROUND: A detailed pathology report is important in the determination of treatment options and prognosis in breast cancer. Australia's first National Cancer Consensus Conference, held in 1994, recommended guidelines for the standardization of the clinical information to be provided to the pathologist, the specifications relating to the handling of specimens, and the resultant pathology report. METHODS: We examined the current status of pathology reporting in invasive breast cancer in three New South Wales hospitals from 1986 to 1994. RESULTS: Histopathologic type was documented in 99% of reports, grade was documented in 47%, size in 46%, and lymph node status in 98%. Only 27% of pathology reports reviewed documented the status of all the above parameters in the one report. Other features such as lymphatic and vascular invasion were documented in only 21% and 9% of pathology reports, respectively, while sex steroid receptor status was reported in almost 90% of cases. CONCLUSIONS: In view of the wide range in the percentage of features reported, we recommend the use of a standardized checklist for the pathological assessment of surgically resected invasive breast cancer specimens.

Wilkinson, N. W., A. Shahryarinejad, et al. (2003). "Concordance with breast cancer pathology reporting practice guidelines." J Am Coll Surg **196**(1): 38-43.

BACKGROUND: Accurate pathology reporting is important for treatment of breast cancer. The College of American Pathologists (CAP) distributed guidelines for reporting cancer specimens in 1998. The aim of this study was to determine community-wide concordance with CAP breast cancer reporting guidelines. STUDY DESIGN: Pathology reporting of stage I and II breast cancers was examined for adherence to CAP guidelines. Pathology reports were reviewed from 100 consecutive cases of invasive breast cancers referred to Roswell Park Cancer Institute in 1998 to 1999 from community hospitals after excisional breast biopsy and 20 consecutive cases with excisional biopsy at RPCI. Adherence to CAP guidelines for clinically relevant items was determined from the original pathology report in each case. RESULTS: One hundred one cases met the inclusion criteria. Most reports did not include at least one of the guideline required elements. Surgical margins were inked in only 77%, and the margins oriented in only 25% of patients. Many specimens were not oriented by the surgeon. Grade was reported in most cases, but the Bloom Scarf Richardson grade was reported in only 6%. The presence or absence of lymphovascular invasion, and of coexisting in situ disease, was reported in 57% and 71%, respectively. The extent and type of in situ disease was reported in 47% and 49%, respectively. CONCLUSIONS: Breast cancer pathology reporting varies widely. Key elements that affect treatment are often omitted. These include gross description and size, orientation and involvement of surgical margins, and description of histologic features, including Bloom Scarf Richardson reporting of grade and the extent of an in situ component. Passive distribution of CAP practice guidelines might be insufficient to accomplish community-wide quality improvement in breast pathology reporting.

Williams, H. and I. J. Powell (2009). "Epidemiology, pathology, and genetics of prostate cancer among African Americans compared with other ethnicities." Methods Mol Biol **472**: 439-53.

Prostate cancer is the most common cancer affecting men in the Western world. In the United States, it is the second leading cause of cancer related deaths after lung and bronchus carcinoma. No definitive causes of prostate cancer (PCa) have been identified to date but, increasing age, a positive family history, and sub-Saharan African ancestry are strongly linked to its development. African American men (AAM) have the highest reported incidence rates in the United States and their mortality from the disease is markedly higher than that of European American men (EAM). Conversely, Asian American men and Pacific Islanders (API), American Indian and Alaskan Native (AI/AN) men, and Hispanic men all have lower incidence and mortality rates as compared with EAM. The reasons for these differences are unclear. However, it is clear that AAM have more advanced PCa when diagnosed. Several other reasons have been suggested and these include differences in treatments and health seeking behavior among the ethnic groups, cultural beliefs, environmental/lifestyle factors, dietary and genetic factors. In conclusion, there are multiple factors that impact prostate cancer outcome and that may be responsible for ethnic disparity. These factors are discussed in this chapter.

Witjes, J. A., L. A. Kiemeney, et al. (1994). "The influence of review pathology on study outcome of a randomized multicentre superficial bladder cancer trial. Members of the Dutch South East Cooperative Urological Group." Br J Urol **73**(2): 172-6.

OBJECTIVE: To determine whether differences between local and review pathology in a multicentre study influence the results of treatment and results from prognostic factor analysis. PATIENTS AND METHODS: A randomized multicentre study in superficial bladder cancer is reported, in which the influence of local and review pathology on the study outcome was investigated. RESULTS: The conformity between local and review pathology of the pT category was 79.3%, of the grade 70.2%, and the combination of both 59.7%. In local pathology, undergrading was more frequent than overgrading and overstaging more frequent than understaging. However, the risks of recurrent disease in the separate stage and grade groups remained the same after correcting the pathology result. A prognostic factor analysis with regard to the risk of recurrent disease was carried out. The Cox hazard ratios of tumour localization, multiplicity, patient age (significant factors), tumour grade, size, history and gender (not significant) remained almost the same after correction for review pathology. Only the prognostic relevance of tumour stage increased after pathology correction. CONCLUSION: We conclude that, although review pathology caused considerable changes in the pathology results, this did not change the results of treatment, and hardly altered the results of a prognostic factor analysis in this randomized study.

Witjes, J. A., P. M. Moonen, et al. (2006). "Review pathology in a diagnostic bladder cancer trial: effect of patient risk category." Urology **67**(4): 751-5.

OBJECTIVES: Bladder cancer pathologic features are a continuous spectrum from benign to invasive lesions, causing diagnostic difficulties. Review pathology might be an answer, but appears to be of limited value. We studied the effect of patients'

risk profile on the value of review pathology. METHODS: We used three Phase III multicenter studies that assessed the value of hexaminolevulinate fluorescence cystoscopy on diagnosis and management. Two studies (Europe and United States) included patients at high risk of carcinoma in situ (CIS), the third study (Europe) included all patients at risk of bladder cancer. Tumors and biopsies were examined by a local and review pathologist. RESULTS: The percentage of patients with CIS was high in the first two studies (20.6% and 15.9%) compared with the epidemiologic data (7.9%) and the third study (7.8%). The numbers of patients (specimens) in the three studies were 209 (927), 277 (986), and 142 (553). Overall conformity for both grade and stage was between 50.5% and 56.6%, comparable to published data. Although conformity was best in the high-risk study, this was predominantly because of the better conformity in low-risk tumors. Conformity in Stage T1, CIS, and invasive tumors was low. The results from Europe and the United States were comparable, although the local pathologist in the United States tended to overstage or overgrade. CONCLUSIONS: Although histologic conformity was greater in the high-risk patient population, this was mainly a result of pTa tumors. The diagnosis of pT1, CIS, and invasiveness appears difficult. Because these tumors significantly influence therapy, review pathology in patients at high risk or suspicious for high risk should be considered.

Wong, S. K., B. B. Jalaludin, et al. (2008). "Tumor pathology and long-term survival in emergency colorectal cancer." Dis Colon Rectum **51**(2): 223-30.

PURPOSE: Patients who have an emergency operation for colorectal cancer have poorer long-term survival outcomes compared with elective patients. This study was designed to define the role of tumor pathology as a basis for the differences in survival outcomes. METHODS: There were 1,537 elective and 286 emergency patients who had an operation for bowel cancer from 1997 to 2003. Tumor pathology and survival data collected prospectively for these patients were compared by modes of presentation. RESULTS: Excluding 30-day mortality, emergency patients as a whole had a five-year all-cause survival rate of 39.2 percent compared with 64.7 percent for elective patients P<0.0001 they also had more advanced Dukes C and D tumors (P<0.0001). The rates of early T1 and T2 cancers were 4.7 percent for the emergency and 25 percent for the elective group. Emergency cases had more lymph node-positive patients and N2 patients (57.1 vs. 41.8 percent and 26.6 vs. 15.9 percent, respectively; P<0.0001). Curatively resected emergency colon patients again had more advanced Dukes staged tumors (P<0.0001) with a five-year survival rate of 51.6 percent compared with 75.6 percent for elective patients P<0.0001. On stage-for-stage analysis, the survival rates for curatively resected Dukes B and C colon cancers remained worse for emergency patients (P=0.003 and P=0.0002, respectively). Both emergency Dukes B and C groups had more T4 cases (21.5 vs. 10.6 percent; P=0.017 and 26.4 vs. 15 percent; P=0.016, respectively). CONCLUSION: Advanced tumor pathology is a basis for poor long-term survival in emergency colorectal cancers.

Yang, W. T., T. H. Cheung, et al. (1999). "Comparison of laparoscopic sonography with surgical pathology in the evaluation of pelvic lymph nodes in women with cervical cancer." AJR Am J Roentgenol **172**(6): 1521-5.

OBJECTIVE: This study compared laparoscopic sonography with surgical pathology in the evaluation of pelvic lymph nodes in women with cervical cancer. SUBJECTS AND METHODS: Intraoperative laparoscopic sonography of pelvic lymph nodes was performed in 31 women with biopsy-proven cervical cancer. A lymph node that was rounded (longitudinal-transverse axis ratio of <2) or showed absence of central hilum was defined as positive for metastasis. For comparison, lymph nodes from each hemipelvis were grouped anatomically into paraaortic, common, internal, and external iliac chains during evaluation on laparoscopic sonography and on surgical pathologic examination. RESULTS: Pelvic dissection in 31 women yielded 630 lymph nodes. There were 54 metastatic nodes in 12 women. Laparoscopic sonography revealed 32 (59%) of all pathologically metastatic lymph nodes. Sensitivity on laparoscopic sonography when comparing groups by hemipelves was 93.3% and by anatomic lymph node chains was 76.2%. Metastatic nodes were most commonly located in the common iliac region and were characteristically rounded, hypoechoic, showed absence of central hilum, and occasionally showed central necrosis. Nine (28%) of 32 metastatic lymph nodes revealed by laparoscopic sonography measured 1 cm or less. Six benign nodes in four patients were also visualized with laparoscopic sonography. CONCLUSION: Laparoscopic sonography achieved a sensitivity exceeding 90% in the detection of metastatic lymph nodes in the hemipelves of women with cervical cancer. Laparoscopic sonography is a feasible and promising technique for the evaluation of pelvic lymph nodes in women with cervical cancer and merits further evaluation.

Yao, M., P. Luo, et al. (2007). "Pathology and FDG PET correlation of residual lymph nodes in head and

neck cancer after radiation treatment." Am J Clin Oncol **30**(3): 264-70.

BACKGROUND: This study determines if postradiotherapy [18F]fluorodeoxyglucose positron emission tomography (FDG PET) can predict the pathology status of residual cervical lymph nodes in patients undergoing definitive radiotherapy for head and neck squamous cell carcinoma (HNSCC). METHODS: Patients with stage N2 or higher HNSCC underwent PET and CT imaging after definitive radiotherapy. Patients with radiographically persistent lymphadenopathy underwent either neck dissection or fine needle aspiration (FNA) of the lymph nodes under ultrasound guidance. PET scan results were correlated with the pathologic findings of the residual lymphadenopathy. RESULTS: Twenty-four hemi-necks in 23 patients with residual lymphadenopathy had neck dissection or FNA. The pathology correlated strongly with the post-RT FDG PET studies. All patients with a negative post-RT FDG PET and those with a maximum standardized uptake value (SUVmax) of less than 3.0 in the post-RT FDG PET were found to be free from residual viable tumor. Using a SUVmax of less than 3.0 as the criterion for a negative FDG PET study, the sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 84.2%, 62.5%, and 100%, respectively. CONCLUSIONS: A negative post-RT FDG PET is very predictive of negative pathology in the residual lymph node after definitive radiotherapy for advanced HNSCC. A prospective clinical trial is warranted to determine if neck dissection can be withheld in these patients.

Yasui, W., N. Oue, et al. (2009). "Transcriptome dissection of gastric cancer: identification of novel diagnostic and therapeutic targets from pathology specimens." Pathol Int **59**(3): 121-36.

Gastric cancer is the fourth most common malignancy in the world, and mortality due to gastric cancer is second only to that from lung cancer. 'Transcriptome dissection' is a detailed analysis of the entire expressed transcripts from a cancer, for the purpose of understanding the precise molecular mechanism of pathogenesis. Serial analysis of gene expression (SAGE) is a suitable technique for performing transcriptome dissection. Gastric cancers of different stages and histology were analyzed on SAGE, and one of the largest gastric cancer SAGE libraries in the world was created (GEO accession number GSE 545). Through SAGE, many candidate genes have been identified as potential diagnostic and therapeutic targets for the treatment of gastric cancer. Regenerating islet-derived family, member 4 (Reg IV) participated in 5-fluorouracil (5-FU) resistance and peritoneal metastasis, and its expression was associated with an intestinal phenotype of gastric cancer and with endocrine differentiation. GW112 expression correlated with advanced tumor stage. Measurement of Reg IV and GW112 levels in sera indicated a sensitivity of 57% for detection of cancer. SPC18 participated in tumor growth and invasion through transforming tumor growth factor-alpha upregulation. Palate, lung, and nasal epithelium carcinoma-associated protein (PLUNC) was a useful marker for gastric hepatoid adenocarcinoma. Expression of SOX9, HOXA10, CDH17, and loss of claudin-18 expression were associated with an intestinal phenotype of gastric cancer. Information obtained from transcriptome dissection greatly contributes to diagnosis and treatment of gastric cancer.

Yunker, W. K., T. W. Matthews, et al. (2008). "Making the most of your pathology: standardized histopathology reporting in head and neck cancer." J Otolaryngol Head Neck Surg **37**(1): 48-55.

OBJECTIVES: Inconsistencies in pathology reporting can contribute to treatment delays and, potentially, inadequate or inappropriate postoperative therapy for patients with malignant disease. Given their importance, there is growing interest in optimizing the reproducibility and readability of pathology reports. The purpose of this study was twofold: (1) to assess the quality and completeness of current head and neck pathology reports in the Calgary Health Region and (2) to examine the effects of a standardized pathology report on clinician comprehension and proposed patient management. METHODS: A retrospective review examining the quality and completeness of current head and neck pathology reports was conducted. This was followed by a prospective survey of Canadian head and neck surgeons. Participants were asked to read a traditional freeform pathology report and a standardized pathology report and then complete a brief questionnaire. Comparisons between the responses were then made. RESULTS: Our retrospective analysis demonstrated considerable variation in the completeness of current freeform head and neck pathology reports. The results from our prospective survey establish that our standardized pathology report required significantly less time to read and was preferred by the majority of respondents. In addition, comprehension tended to be higher after reading the standardized pathology report. CONCLUSION: Standardized pathology reports are known to enhance report quality and consistency. We demonstrate in this study that they require less time to read, are better received, and do not negatively impact reading comprehension, potentially making them an effective

and feasible alternative to traditional, freeform pathology reports.

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