In patients with early breast cancer, the 10-year disease-free survival rate is significantly improved for those with low competing mortality risk scores versus high scores.

**Objective:** To determine predictors of competing mortality risks among patients with early breast cancer.

**Design:** Multicenter study.

**Methods:** The authors conducted a prospective study to evaluate outcomes of patients with stage I to II breast cancer treated with breast-conserving surgery plus radiation therapy. Exclusion criteria included mastectomy treatment, omission of radiation therapy, bilateral breast cancer, or history of another cancer within 10 years. Disease-free survival was estimated using the Kaplan-Meier method. The competing mortality risk score was derived from age, race, and comorbidities.

**Results:** The authors identified 1231 patients from 3 centers who met the inclusion criteria. The mean tumor size was 1.55 cm. Sixty-nine percent of patients had stage I disease, and 18% had lymph node metastases. Black race was associated with low socioeconomic status, comorbid illness, larger tumor size, and estrogen receptor-negative tumors. The overall 10-year disease-free survival rate was 69.7%. The 10-year cumulative incidence of locoregional recurrence, distant recurrence, and competing mortality was 4.4%, 7.1%, and 18.7%, respectively. On multivariate analysis, worse disease-free survival was significantly associated with increasing age, black race, comorbid disease, lymph node metastases, tumor size, and mammographic detection. Patients with a low versus high competing mortality risk score had a significantly decreased risk of competing mortality (7.2% vs 30.6%). The 10-year disease-free survival rate was significantly improved for patients with low competing mortality risk scores versus high scores (79.3% vs 59.4%).

**Conclusions:** The authors conclude that competing mortality is an important event that influences disease-free survival rates; increasing age, black race, and comorbid disease are associated with competing mortality.

**Reviewer's Comments:** These findings suggest that clinical trial design and analysis should include cancer-specific and noncancer-specific outcomes. In addition, improved medical care should be directed to those patients with high competing mortality scores. (Reviewer-Todd M. Tuttle, MD).

Keywords: Early Breast Cancer, Competing Mortality Risks, Predictors

Print Tag: Refer to original journal article
Triple-negative breast cancer patients have a poorer survival rate than patients with other breast cancer subtypes during the first 3 to 5 years following diagnosis, but after 10 years, they are less likely to relapse than estrogen receptor-positive patients.

**Background:** The triple-negative phenotype (tumors lacking estrogen receptor [ER], progesterone receptor [PR], and HER2 expression) is diagnosed in 12% to 17% of breast cancer patients. While triple-negative (a.k.a. basal-like) breast cancer is frequently associated with an aggressive course and poor response to treatment, long-term survival is possible, and late relapse is less likely than in ER-positive patients.

**Objective:** To review the literature on triple-negative breast cancer.

**Design:** Literature review.

**Results:** Triple-negative and basal-like are not totally synonymous terms. Basal-like cancers originally identified by microarray analysis express genes found in basal or myoepithelial cells and may express ER at low levels. From 18% to 40% of basal-like cancers are not phenotypically triple-negative, while approximately 80% of triple-negative cancers are basal-like. Triple-negative and basal-like cancers are usually high grade. Patients are more often young black or Hispanic women than members of other ethnic groups, and overlap with BRCA1 mutations is about 75%. Increasing parity and higher waist-to-hip circumference ratio increase the risk of basal-like cancer. For more common breast cancer types, risk decreases with increasing parity. Basal-like cells resemble cancer stem cells when they undergo epithelial-to-mesenchymal transition, a normal cell function involved in wound healing that likely confers metastatic potential on cancer cells. Larger size, node negativity, and high-grade histology are frequent triple-negative and basal-like tumor features. Primary tumor size and survival are less closely related than with other breast cancer types. Despite the biologic aggressiveness of their tumors and a poor prognosis during the first 3 to 5 years, patients with triple-negative and basal-like cancers are less likely than those with other types to suffer late relapse beyond 5 years, and many are potentially curable. Chemotherapy outcomes for triple-negative patients are generally poorer than for other breast cancer types, but triple-negative patients benefit more from chemotherapy than do those with ER-positive tumors. Even though there is no established standard chemotherapy regimen for triple-negative breast cancer, the literature supports anthracycline/taxane combinations. Neoadjuvant cisplatin combinations produce high complete pathologic response rates, and ixabepilone has shown promise in early trials. Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors combined with chemotherapy have shown impressive results in phase 2 trials involving triple-negative patients.

**Conclusions:** The authors conclude that triple-negative and basal-like breast cancers represent a heterogeneous group that, despite a typically aggressive course and poor prognosis, respond to chemotherapy and are potentially curable in many cases.

**Reviewer’s Comments:** State-of-the-art triple-negative and basal-like breast cancer management relies on the use of chemotherapy with taxane/anthracycline or platinum combinations. Ixabepilone and PARP inhibitors hold promise for the future. (Reviewer-Alan B. Grosbach, MD).

**Keywords:** Triple-Negative Breast Cancer, Basal-Epithelial Phenotype, Survival, Prognosis

**Print Tag:** Refer to original journal article
Seed localization may be a useful alternative to wire localization for nonpalpable breast lesions.

**Objective:** To determine the feasibility of seed localization for nonpalpable breast lesions in a public health care delivery system.

**Design:** Retrospective, single-center study.

**Participants/Methods:** The authors conducted a retrospective review of all patients at their institution who underwent partial mastectomy between 2005 and 2010. For localization of nonpalpable breast lesions, an I125 radioactive seed was placed using either sonographic or mammographic guidance. The lesion was identified with the aid of a handheld gamma counter intraoperatively. Specimen radiography was performed to confirm the presence of the seed and to identify its location from the margins. Matched-pair analysis was performed between patients who underwent wire localization versus seed localization. The 2 groups were matched for tumor size, histology, neoadjuvant chemotherapy, and percent of ductal carcinoma in situ (DCIS).

**Results:** 50 seed localizations were successfully performed. Of these, 33 patients had either invasive breast cancer or DCIS; 17 had benign disease. Among the 33 patients with invasive carcinoma or DCIS, 14 patients required reoperation, 10 had positive margins, and 4 had close margins (<2 mm). Six patients eventually underwent mastectomy. As compared to patients who underwent wire localization, the re-excision rate was slightly decreased for patients undergoing seed localization (42% vs 54%; not statistically significant). There were no cases of seed migrations. Specimen radiography demonstrated excision of the targeted lesion in 100% of cases.

**Conclusions:** The authors conclude that seed localization is a useful alternative to wire localization for nonpalpable breast lesions. This procedure is feasible in a county-based population composed primarily of minority and low-income patients.

**Reviewer’s Comments:** This study demonstrates that seed localization is feasible. However, in this matched-pair analysis, the re-excision rates were not significantly different. Some studies have demonstrated that seed localization is associated with removal of less breast volume as compared with wire localization; volume of excision was not measured in this study. (Reviewer-Todd M. Tuttle, MD).

Keywords: Nonpalpable Breast Lesions, Seed Localization, Public Health Care

Print Tag: Refer to original journal article
A high percentage of patients with advanced, previously treated cancers have tumors that retain identifiable treatment targets through the use of molecular profiling.

**Background:** In 2006, Von Hoff et al demonstrated that tumors from a substantial percentage of patients with pretreated, refractory cancers harbor potential targets for standard chemotherapy.

**Objective:** To compare progression-free survival (PFS) from individually targeted therapy based on molecular profiling (MP) with that of the most recent empiric treatment.

**Design:** Prospective multicenter single-arm trial.

**Participants:** 86 patients with advanced, previously treated cancer, an ECOG performance status of 0 to 1, and the ability to undergo a biopsy.

**Methods:** Tumor biopsy specimens were analyzed by oligonucleotide microarray (MA) and immunohistochemistry (IHC)/fluorescent in situ hybridization (FISH). Patients served as their own controls with the comparison of PFS on their most recent therapy with that on therapy suggested by MP.

**Interventions:** 66 of the 86 patients received chemotherapy, hormone therapy, or targeted therapy (cetuximab, sunitinib) based on MP.

**Results:** The most frequent tumor types among treated patients were breast (n=18), colorectal (n=11), and ovarian (n=5). There were 43 women and 23 men. The median age was 60 years (range, 27 to 75 years). Of the 66 patients, 18 (27%) had a PFS ratio ≥1.3 when their MP profile-suggested treatment outcomes were compared with the most recent previous treatment (P=0.007). The median PFS survival ratio was 2.9. Eight of the 18 patients with a PFS ratio ≥1.3 had breast cancer (1 complete and 2 partial responses), 4 patients had colorectal cancer (1 partial response), and 1 patient each had ovarian cancer (partial response), non–small-cell lung cancer (partial response), cholangiocarcinoma, mesothelioma, eccrine sweat gland tumor, and gastrointestinal stromal tumor. MP yielded targets for 84 (98%) of the 86 tumors tested; 83 of the 86 by IHC/FISH and 81 of the 86 by MA. Patients with a PFS ratio ≥1.3 had a median PFS of 9.7 months compared with 5 months for the entire group of 66 (P=0.026), indicating a correlation between PFS ratio and survival. No relationship was observed between the treatment that clinicians would have chosen and that suggested by MP.

**Conclusions:** PFS is longer for an MP-suggested regimen than the clinician-selected treatment. This technique is feasible even when tumor specimens require shipment to a distant site.

**Reviewer's Comments:** PFS ratios represent a novel parameter of clinical effectiveness; however, since subsequent responses in advanced cancer are typically shorter, not longer, these results are impressive. (Reviewer-Alan B. Grosbach, MD).

Keywords: Oligonucleotide Microarray Gene Expression Assay, Molecular Profiling

Print Tag: Refer to original journal article
Mutations of the **EGFR** gene are present in 15% of non–small cell lung cancers and are associated with adenocarcinomas. On the other hand, overexpression of EGFR is common in squamous cell cancers.

**Background:** Lung cancer is the leading cause of cancer-related deaths worldwide, and non–small cell lung cancer (NSCLC) accounts for 85% of lung cancers. Until recently, NSCLC was treated as a single entity and histology did not matter. Treatment strategies were based only on tumor stage. Advances have led to molecularly charged agents, including those targeting vascular endothelial growth factors (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factor I (IGF-1) signaling.

**Objective:** To review the molecular mechanisms underlying NSCLC histology and how we can use this knowledge to tailor therapy.

**Results:** In Western countries, there has been an increased incidence of adenocarcinoma, particularly bronchoalveolar carcinoma (BAC), and decreased incidence of squamous cell cancer, which probably reflects decreased smoking. Most adenocarcinomas are thyroid transcription factor 1 (TTF1) positive, and metastatic adenocarcinomas are TTF1 negative. Mucinous BAC are generally TTF1 negative and CK20 positive. Squamous cell cancers display markers reflective of keratinization (+CK5, +CK6) as well as p63. Large cell cancers comprise around 5% of lung cancers and have neither squamous nor glandular differentiation. Large-cell carcinomas have neuroendocrine differentiation, and half of these tumors are +TTF1. **TP53, RB, p16INa4a, and 8p21-23 changes** occur more frequently in squamous cell tumors than adenocarcinomas. The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway transduces several receptor tyrosine kinases (RTK) including EGF receptor (EGF-R), IGF-1 receptor (IGF-1R), stem-cell factor receptor (KIT) and c-MET. IGF-1R is more prominently expressed in squamous cell cancers. Mutations of the **EGFR** gene are present in 15% of NSCLC and are associated with adenocarcinomas. On the other hand, overexpression of EGFR is common in squamous cell cancers. **KRAS** mutations are common in tumors with wild-type EGFR, usually adenocarcinomas, and may confer resistance to growth factor receptor inhibitors.

**Approved Drugs:** Bevacizumab has been approved for use in addition to platinum-based first-line therapy for nonsquamous histology. Squamous histology is associated with increased risk of pulmonary hemorrhage. Pemetrexed, a multitargeted folate antimetabolite, is approved in first-line, maintenance, and second-line roles for nonsquamous NSCLC histologies.

**Reviewer’s Comments:** One of the real questions in my mind is the ability of pathologists to accurately and reproducibly get the histologic subtype correct. In their defense, many tumors are mixed and pathologists must choose the dominant subtype. Also, many are very poorly differentiated, again complicating accurate histologic subtyping. (Reviewer-Jonathan J. Beitle, MD, MBA).

Keywords: Advanced NSCLC, Histology, Targeted Therapy

Print Tag: Refer to original journal article
Combined Staging Saves Patients Unnecessary Thoracotomy

*Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial.*

Annema JT, van Meerbeeck JP, et al:

JAMA 2010; 304 (November 24): 2245-2252

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**Background:** Surgical resection for lung cancer is the treatment of choice if the mediastinal nodes are negative and there are no distant metastases. With positive mediastinal nodes in non–small-cell lung cancer (NSCLC), combined modality treatment is the treatment of choice. CT is the modality of choice for assessing the primary tumor, and PET scanning is valuable for detecting metastatic disease. The workup of the mediastinum includes a PET/CT followed by biopsy, as PET-positive intrathoracic nodes are, by themselves, inaccurate. Mediastinoscopy has 78% sensitivity. Mediastinal lymph nodes can also be sampled using real-time ultrasound guidance from either a transesophageal ultrasound-guided fine-needle aspiration (EUS-FNA) or transbronchially by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Combined EBUS and EUS have a reported sensitivity of 93%.

**Objective:** To compare surgical staging alone versus endosonography followed by surgical staging. Surgical staging was felt to be the gold standard, and this international group felt that a surgery versus endosonographic staging trial was not possible.

**Design/Methods:** A prospective, randomized trial was carried out between 2007 and 2009 by 4 institutions in the Netherlands and Great Britain. The primary end point was sensitivity of detection of mediastinal nodes by either staging strategy, with thoracotomy with nodal dissection being the reference standard.

**Interventions:** Potentially resectable patients were randomly assigned to surgical staging alone or combined EBUS-TBNA and EUS-FNA followed by surgical staging if the endosonographically identified nodes were pathologically negative. Mediastinoscopy was performed according to current guidelines and, if deemed necessary, a left parasternal mediastinotomy or video-assisted thoracoscopy was performed in addition to the mediastinoscopy.

**Results:** With 241 patients randomized, both groups were well-balanced. Mediastinal metastases were found by mediastinoscopy alone in 35% of the patients. In 70 patients who had thoracotomy, nodal metastases were found in 10 patients. For the other arm, endosonography detected mediastinal nodes in 46% of the patients. Mediastinoscopy after negative endosonographic staging detected mediastinal disease in 6 additional patients. In the 58 patients without mediastinal disease by endosonographic staging or mediastinoscopy, 4 patients had mediastinal disease at thoracotomy. For the mediastinoscopy only patients, nodal metastases were found in 10 patients, and for the endosonography patients who also underwent mediastinoscopy, there were 4 patients with mediastinal nodes that were missed. The sensitivity for mediastinoscopy only and for endosonography plus mediastinoscopy was 79% and 94%, respectively. The negative predictive value for mediastinoscopy alone was 86% and 93% for the combination of endosonographic staging followed by mediastinoscopy. The number of unnecessary thoracotomies was 21 (18%) in the mediastinoscopy-only group and 9 (7%) in the combined staging group.

**Conclusions:** Combined staging with the addition of endosonography saved 14% of patients an unnecessary thoracotomy.

**Reviewer's Comments:** Endoscopic staging has earned its place in the workup of NSCLC patients. At my institution, the excellent pulmonologists who do the endoscopic workup have joined general thoracic surgery. (Reviewer-Jonathan J. Beitler, MD, MBA).

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Keywords: Lung Cancer, Mediastinoscopy Nodal Staging
The overall recurrence rate is significantly higher in patients with hepatocellular carcinoma who undergo radiofrequency ablation versus resection.

**Objective:** To compare outcomes of surgical resection versus radiofrequency ablation (RFA) for treatment of hepatocellular carcinoma (HCC).

**Design:** Prospective, randomized clinical trial.

**Participants/Methods:** The authors recruited patients with HCC who met Milan criteria for liver transplantation. Inclusion criteria were single HCC ≤5 cm or up to 3 nodules, with each nodule <3 cm, no extrahepatic metastasis or vascular invasion, no previous treatment of HCC, and disease treatable by either resection or RFA. Exclusion criteria were severe portal hypertension or a patient's willingness to undergo transplantation. The primary end point was overall survival; secondary end points were recurrence-free survival and overall recurrence. RFA was performed with a percutaneous approach.

**Results:** From 2003 to 2005, the authors recruited 115 eligible patients in each group. Baseline characteristics were similar between the 2 groups, except that solitary tumor size was slightly smaller in the resection group. In the resection group, an additional 16 lesions were identified in 15 patients with intraoperative exploration. The length of hospital stay was significantly longer in the resection group. The treatment-related mortality rate was 0% in both groups. Adverse events were significantly more frequent in the resection group. The 5-year overall survival rates were significantly improved in the resection group as compared to the RFA group (76% vs 55%). The 5-year recurrence-free survival rates were also significantly improved in the resection group as compared to the RFA group (51% vs 29%). Type of intervention, age, serum α-fetoprotein (AFP) levels, and tumor number were significantly associated with overall survival. The overall recurrence rate was significantly higher in the RFA group as compared to the resection group.

**Conclusions:** The authors conclude that surgical resection may provide improved survival and lower recurrence rates for HCC as compared with RFA.

**Reviewer's Comments:** Despite the increased early complication rate, resection seems to provide improved oncologic outcomes for patients with HCC who meet Milan criteria for transplantation. Perhaps, treating occult hepatic disease identified at surgery, but not apparent with percutaneous RFA, partially explains these findings. (Reviewer-Todd M. Tuttle, MD).

Keywords: Hepatocellular Carcinoma, Surgical Resection, Radiofrequency Ablation

Print Tag: Refer to original journal article
Laparoscopic Resection Is a Favorable Alternative to Open Liver Resection

Laparoscopic Resection of Colorectal Liver Metastases: Surgical and Long-Term Oncologic Outcome.

Kazaryan AM, Marangos IP, et al:

Ann Surg 2010; 252 (December): 1005-1012

The 5-year actuarial overall survival rate after laparoscopic liver resection is 51%.

Objective: To determine the immediate and long-term outcomes after laparoscopic liver resection for colorectal metastases.

Design: Retrospective single-center study.

Participants/Methods: The authors identified patients at their institution who underwent laparoscopic liver resection for colorectal metastases from 1998 to 2010. Overall survival was estimated from first liver resection until death. Recurrence-free survival was estimated from the first liver resection. Survival rates were compared to those predicted by the Fong and Basingstoke Predictive Index scoring systems.

Results: The authors performed 118 procedures; 5 (4.2%) were converted to open surgery because of adhesions or hemorrhage. The median patient age was 59 years. Most resections were either segmental resections or nonanatomic resections; only 6 patients underwent successful laparoscopic hemihepatectomy. The median operative time was 192 minutes. The median blood loss was 300 cc, and blood transfusions were required in 16% of patients. The median hospital stay was 3 days. Postoperative complications occurred in 13.6% of patients; 1 patient died from multiorgan failure. The resection margin was negative in 93.4% of patients. Hepatic recurrence occurred in 42.1% of patients, but there were no port-site recurrences. The 5-year actuarial overall and disease-free survival rates were 51% and 42%, respectively. The observed survival rates were better than predicted by the Fong and Basingstoke Predictive Index scores. No differences in survival rates were observed between anatomic and nonanatomic liver resections.

Conclusions: The authors conclude that laparoscopic resection is a favorable alternative to open liver resection for patients with colorectal metastases.

Reviewer’s Comments: Improvements in laparoscopic instrumentation have enabled laparoscopic liver resection. The results from this study should be interpreted with caution because only approximately 5% of patients underwent hepatic hepatectomy; most resections were segmental or nonanatomic resections. (Reviewer-Todd M. Tuttle, MD).

Keywords: Colorectal Liver Metastases, Laparoscopy, Anatomic vs Nonanatomic

Print Tag: Refer to original journal article
A combination of gemcitabine and oxaliplatin produces better median survivals when compared to best supportive care for patients with unresectable gallbladder cancer.

**Background:** Gallbladder cancer (GBC) is the most common biliary cancer, but is relatively rare. However, within Northern India, it is relatively common among women. In Delhi, the age-adjusted incidence is 7.4/100,000, and after breast, cervix, and ovarian cancer among women, it is the fourth most common cancer. Only 10% of the patients are surgical candidates. Most series mix various biliary tract cancers with GBC. There is no standard of care for patients with unresectable GBC.

**Objective:** To compare chemotherapy with best supportive care for a patient population with GBC.

**Design:** Prospective, open-labeled trial from the All India Institute of Medical Sciences in New Delhi.

**Participants:** All patients had biopsy- or fine-needle aspiration (FNA)-proven adenocarcinoma of the gallbladder that was either unresectable or metastatic. The planned sample size was 81 (27 patients per arm) and was based on the median survival of 2 months for best supportive care versus 5.5 months for 5-FU and folinic acid (FUFA). Overall survival was the primary end point.

**Methods:** Patients were randomized to 1 of 3 groups: best supportive care; FUFA; or gemcitabine and oxaliplatin (mGEMOX). Cross-over was not allowed, and it was planned that whenever possible, patients would undergo curative surgery. FUFA was a weekly bolus 5-FU and folinic acid for 30 weeks. mGEMOX was 900 mg/m² of gemcitabine and 80 mg/m² of oxaliplatin on days 1 and 8 every 3 weeks for a maximum of 6 cycles. After 3 cycles, if there was progressive disease, treatment was discontinued. Patients whose treatment was delayed by 3 weeks because of toxicity were taken off the protocol. Response was assessed by CT scans.

**Results:** 82 patients were eligible and randomized with the arms being well balanced. FUFA was given for a median of 12 weeks, and the median number of mGEMOX cycles administered was 6. Thus the median duration of chemotherapy was 12 and 18 weeks, respectively ($P < 0.001$). Median overall survival was 4.5 months for best supportive care, 4.6 months for FUFA, and 9.5 months for mGEMOX ($P = 0.39$). There were 2 complete responses (CRs) in the study (both in the mGEMOX arm) for a CR rate of 7.7% for mGEMOX patients. Two patients in the mGEMOX arm and 1 in the FUFA arm underwent radical cholecystectomy. The CR and partial response (PR) rate for mGEMOX was 30.7%, twice that of FUFA. Include stable disease, and the rate was 69%. In the mGEMOX arm, 4 patients (15%) had transaminitis and 10 patients had grade 3 or 4 myelosuppression.

**Conclusions:** Palliative chemotherapy with mGEMOX is superior to best supportive care and FUFA.

**Reviewer's Comments:** I had no idea that GBC was so regionally prevalent in Northern Indian women. The CR patients are intriguing. (Reviewer-Jonathan J. Beitler, MD, MBA).

**Keywords:** Unresectable Gallbladder Cancer, Chemotherapy, Support Care

**Print Tag:** Refer to original journal article
Prophylactic Laxatives, Antiemetics Improve Opioid Tolerance

Pharmaceutical Interventions Facilitate Premedication and Prevent Opioid-Induced Constipation and Emesis in Cancer Patients.

Ishihara M, Iihara H, et al:

Support Care Cancer 2010; 18 (December): 1531-1538

The risk of nausea and vomiting associated with opioid use decreases sharply after the first week, but constipation is a persistent side effect.

**Background:** Constipation, nausea, and vomiting are common side effects of opioid analgesics, raising the question of how they can best be managed.

**Objective:** To determine the prevalence of constipation, nausea, and vomiting among cancer patients taking opioids and to evaluate the effectiveness of a physician and patient educational effort in alleviating these symptoms.

**Design:** Retrospective record review followed by a prospective educational intervention.

**Participants:** 83 cancer inpatients who received opioids (retrospective, part 1) and 107 cancer inpatients who began opioid therapy (prospective, part 2).

**Methods:** Constipation was defined as no stool for >3 days per week. Nausea and vomiting were recorded if grade 1 or higher (Common Terminology Criteria for Adverse Events v3.0). Physicians received information about opioid side effects, opioid orders were verified, and patients were given instructions designed to inform them about side effect management.

**Results:** Among 47 of 83 patients in part 1 who received laxatives (magnesium oxide alone, 21%; magnesium oxide with pantethine, 40%; sennosides, 21%) along with opioids, the incidence of constipation was 21% compared to 56% in 36 patients who did not receive laxatives (\(P = 0.0024\)). The number of days per week with stools differed significantly between groups (5.6 vs 3.9; \(P = 0.005\)). The combination of magnesium oxide plus pantethine was associated with the lowest constipation risk. On multivariate analysis, laxative prophylaxis provided a >5-fold reduction in the risk of constipation (OR, 5.25 for no laxative vs laxative; \(P = 0.001\)). For 43 of 83 patients who received prophylactic antiemetics (prochlorperazine, 88%; domperidone, 7%), the incidence of vomiting was significantly lower than for the 40 patients who did not receive antiemetics (7% vs 25%; \(P = 0.0339\)), but the difference in the incidence of nausea was not significant (19% vs 38%). Multivariate analysis showed that females were at a significantly increased risk of experiencing nausea and vomiting. The lack of prophylaxis significantly increased the risk of vomiting but not nausea. Interventions resulted in 93% of patients receiving laxatives and 81% receiving antiemetics. Intervention was associated with a 9% incidence of constipation compared to 36% before intervention (part 2 vs part 1; \(P < 0.001\)). The incidence of vomiting decreased from 16% to 4% (\(P = 0.0085\)), but the nausea reduction was not significant (28% vs 8%; \(P = 0.078\)).

**Conclusions:** Laxatives and antiemetics should be prescribed prophylactically along with opioid analgesics. Educational and verification interventions significantly altered laxative and antiemetic prescribing.

**Reviewer’s Comments:** The bottom line from this study is that prophylactic laxatives and antiemetics improve opioid tolerance, which should improve opioid compliance and pain control. (Reviewer-Alan B. Grosbach, MD).

Keywords: Opioid Analgesic, Constipation, Nausea/Vomiting, Prophylaxis, Laxatives, Antiemetics

Print Tag: Refer to original journal article
Chronic lymphocytic leukemia patients with del(17p) have the shortest overall survival of any genetic subgroup, with a median survival of 20 and 34 months when treated with chemotherapy and chemoimmunotherapy, respectively.

**Background:** Alkylating agent/purine analog combinations improve response rates and progression-free but not overall survival in patients with chronic lymphocytic leukemia (CLL). Rituximab has produced better outcomes in phase 2 trials.

**Objective:** To compare the efficacy and safety of fludarabine plus cyclophosphamide with or without rituximab in treatment-naïve CLL patients.

**Design:** Multinational prospective randomized phase 3 trial.

**Participants:** Previously untreated Binet stage C CLL patients (252) or those with stage A (40) and B (522) with active disease, ECOG performance status 0 to 1, and low comorbidities.

**Methods:** Disease assessments were performed at baseline, at 1 and 3 months, then every 3 months for the first 3 years, every 6 months during years 4 and 5, and then annually to year 8.

**Interventions:** 6 cycles of fludarabine (25 mg/m² per day) plus cyclophosphamide (250 mg/m² per day) on days 1 to 3 every 28 days with (chemoimmunotherapy group) or without (chemotherapy group) rituximab 375 mg/m² on day 0 (1st cycle) and 500 mg/m² on day 1 (cycles 2 to 6). Growth factor and antiviral prophylaxis were not recommended, but anti-pneumocystis prophylaxis was advised for severe leukopenia lasting >7 days.

**Results:** Chemoimmunotherapy patients had significantly higher rates of complete and overall response (44% vs 22%, and 90% vs 80%; \(P < 0.0001\) for both). Similar results were observed in all stages and age groups as well as in groups with unfavorable cytogenetics and mutated (favorable) and unmutated (unfavorable) immunoglobulin heavy chains. Median progression-free survival (PFS) was 19 months longer with chemoimmunotherapy (51.8 vs 32.8 months; \(P < 0.0001\)). Chemoimmunotherapy patients had better overall survival (OS), with a 33% reduction in the risk of death (\(P = 0.012\)) and a 15.7 month difference in time to 25% of patients dying (62.5 vs 46.8 months; \(P = 0.012\)). Subgroup analysis revealed significantly better PFS and OS for chemoimmunotherapy patients with stage B but not stage A or C disease. Patients with unfavorable cytogenetics--del(17p), del(11q), del(13q), or trisomy 12--had significantly better PFS when treated with chemoimmunotherapy, but only del(11q) and del(13q) patients had significantly better OS. Del(17p) was significantly associated with shorter PFS and OS. Leukopenia and neutropenia were more frequent in the chemoimmunotherapy group (24% vs 12% and 34% vs 21%; \(P < 0.0001\) for both) but other adverse event rates were similar.

**Conclusions:** Rituximab combined with fludarabine and cyclophosphamide significantly improves outcomes (including overall survival) for previously untreated, physically fit CLL patients.

**Reviewer's Comments:** The authors suggest that since patients with del(17p) had the poorest prognosis and derived the least benefit from chemoimmunotherapy, they should be considered for allogenic stem cell transplant if physically fit. (Reviewer-Alan B. Grosbach, MD.)

**Keywords:** Rituximab, Fludarabine, Cyclophosphamide, Chronic Lymphocytic Leukemia, Survival

Print Tag: Refer to original journal article
Objective: To compare the outcomes of pure desmoplastic melanoma (PDM) with those of mixed desmoplastic melanoma (MDM).

Design: Retrospective analysis of a single center study.

Participants/Methods: The authors identified 276 patients diagnosed with desmoplastic melanoma from 1977 through 2002 at their institution. Patient, tumor, and outcome data were abstracted from their prospective database. The lesions were classified as PDM if desmoplasia was prominent throughout the tumor (≥80%). The main end points were local recurrence, distant metastasis, and melanoma-specific mortality.

Results: 118 tumors (49%) were classified as PDM and 124 as MDM. The median follow-up was approximately 120 months in both groups. Among the PDM patients, lymph node metastases were identified in 3.4% of cases by either elective lymph node dissection or sentinel lymph node biopsy. Among the patients with MDM, lymph node metastases were identified in 13.7% of cases by elective lymph node dissection or sentinel lymph node biopsy. Among patients with PDM, the risk of local recurrence was increased with 1-cm margins as compared to 2-cm margins. By multivariate analysis, the risk of local recurrence was slightly higher, but not statistically significant, for PDM compared to MDM. The 5-year cumulative incidence of distant metastasis was significantly higher for the MDM than PDM patients on multivariate analysis. Likewise, the overall 5-year survival rate was significantly improved for PDM compared to MDM (79.5% vs 61.3%).

Conclusions: The authors conclude that PDMs, even thin ones, should be treated with 2-cm margins. The clinical behavior of MDMs is similar to non-desmoplastic melanomas.

Reviewer’s Comments: The very low incidence of lymph node metastases from PDM is consistent with previous studies. The role of sentinel lymph node biopsy is not clear for these patients. (Reviewer-Todd M. Tuttle, MD).

Keywords: Desmoplastic Melanoma, Clinical Behavior

Print Tag: Refer to original journal article
Peripheral blood FISH and quantitative PCR testing are highly reliable for monitoring chronic myeloid leukemia treatment in all phases and with both first- and second-line treatments.

**Background:** Peripheral blood testing for BCR-ABL1 via fluorescent in situ hybridization (FISH) and quantitative polymerase chain reaction (Q-PCR) techniques are well established for monitoring imatinib therapy of chronic myeloid leukemia (CML). The preferred technique for monitoring second-line treatment remains undefined.

**Objective:** To compare peripheral blood (PB) and bone marrow (BM) BCR-ABL1 techniques for monitoring second-line CML treatment.

**Design:** Retrospective record review.

**Participants/Methods:** 70 patients with CML in chronic (48), accelerated (11), or blast (11) phase. Patients had undergone simultaneous PB and BM testing for BCR-ABL1 while undergoing treatment with imatinib, nilotinib, dasatinib, bosutinib, or homoharringtonine.

**Results:** The correlation between PB and BM FISH for 61 patients who had 112 FISH analyses was 95%; between PB FISH and BM cytogenetics, this rate was 89% (in 54 patients); PB Q-PCR had an 87% correlation with BM Q-PCR and an 82% correlation with BM cytogenetics for 58 patients. BM Q-PCR and BM cytogenetics had a 78% correlation. The correlations between BM cytogenetics and PB FISH and PB Q-PCR for 18 patients with Philadelphia chromosome variants or additional abnormalities were 71% and 75%, respectively. BM FISH/BM cytogenetic correlation in this same group was 84%. BM and PB FISH correlated in 92% of cases; BM and PB Q-PCR correlated in 89%. Among patients (16) with ABL1 kinase mutations and imatinib-resistant CML, the correlation between BM cytogenetics and PB FISH was 79%, and for PB Q-PCR, this rate was 86%. Correlations between BM and PB FISH and PB and BM Q-PCR in this group were both 95%. The BM FISH and cytogenetics correlation was 93%; the BM Q-PCR and cytogenetics correlation was 84%. There was no instance of a patient achieving complete cytogenetic (BM) remission with positive PB FISH. BM Philadelphia chromosome positivity was detected transiently in 3 patients with negative PB FISH. Semi-annual BM cytogenetics during the first 18 months of follow-up after diagnosis cost $8500 more than PB monitoring ($11,104 vs $2592).

**Conclusions:** PB FISH and Q-PCR provide reliable monitoring of CML therapy in all phases.

**Reviewer's Comments:** These results provide strong support for peripheral blood monitoring of CML treatment in lieu of routine bone marrow biopsies, sparing patients considerable cost and discomfort. (Reviewer Alan B. Grosbach, MD).

Keywords: FISH, PCR, Chronic Myeloid Leukemia, Blood, Monitoring

Print Tag: Refer to original journal article
The majority of men who undergo retroperitoneal lymph node dissection for testis cancer maintain antegrade emission and ejaculation.

**Objective:** To determine the incidence of antegrade emission and ejaculation and fertility following primary retroperitoneal lymph node dissection for testis cancer.

**Participants/Methods:** 280 patients who underwent primary retroperitoneal lymph node dissection for testis cancer were identified. Of this group, 176 were contacted and queried about ejaculatory and fertility status.

**Results:** 171 of 176 (97%) patients reported that they had preserved antegrade emission and ejaculation. Overall, 134 of 135 men who underwent a nerve-sparing procedure could ejaculate as could 33 of 37 (89%) men who underwent non–nerve-sparing surgery. Sixty-four of the men had attempted to father children and 47 (74%) were successful.

**Conclusions:** The authors believe that men who undergo modern primary retroperitoneal lymph node dissection for testis cancer maintain antegrade emission and ejaculation and the majority are able to father children.

**Reviewer's Comments:** Historically, failure of seminal fluid emission following retroperitoneal lymph node dissection for testis cancer was the major morbidity. Surgical techniques have changed and nerve-sparing techniques introduced. The results published in this study from the University of Indiana are exceptionally good. The vast majority of patients continued to have emission and antegrade ejaculation. Somewhat surprisingly, the vast majority of patients who underwent non–nerve-sparing surgery also retained their ability to have seminal fluid emission and to father children. As the authors suggest, because of increasing awareness of the long-term toxicity of chemotherapy, perhaps primary retroperitoneal lymph node dissection for patients with clinical stage I nonseminomatous testis tumors will become more common therapy. It remains to be demonstrated whether other centers can replicate the very good results published in this paper. (Reviewer-George S. Benson, MD).

**Keywords:** Testis Cancer, Retroperitoneal Lymph Node Dissection, Emission, Ejaculation

**Print Tag:** Refer to original journal article
Active Surveillance With IMRT Associated With Highest QALYs

Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer: A Decision Analysis.
Hayes JH, Ollendorf DA, et al:
JAMA 2010; 304 (December 1): 2373-2380

According to a decision analysis, active surveillance is the best choice for 65-year-old men with low-risk prostate cancer.

**Background:** Of the nearly 192,000 men diagnosed with prostate cancer in the U.S., 70% will have low-risk, clinically localized disease. More than 90% will undergo initial treatment with either surgery or radiation, and the majority will suffer at least 1e adverse effect. In the prostate-specific antigen (PSA) era, according to the authors, >60% of men may not require therapy. In the European Randomized Study of Screening for Prostate Cancer, though there was a 20% reduction in mortality, 48 men had to be treated to prevent 1 prostate cancer death. Active surveillance has the potential to mitigate overtreatment.

**Objective:** To perform a decision analysis to assess quality-adjusted life expectancy (QALE) of active surveillance compared with various initial treatment choices for prostate cancer.

**Design:** State transition model analyzed using Monte Carlo simulation: men enter the model at age 65 with low-risk, clinically localized prostate cancer (PSA <10 ng/mL, stage ≤T2a, and Gleason score ≤6).

**Methods:** Theoretical interventions included intensity-modulated radiation therapy (IMRT), brachytherapy, and open retropubic nerve-sparing radical prostatectomy. The active surveillance option includes regular physical examinations, PSA measurements, and rebiopsy 1 year after diagnosis and every 3 years thereafter. Treatment is triggered by progression of PSA to a Gleason score of ≥7, increased PSA, or patient preference. Model inputs were estimated from systemic reviews of the literature. Quality of life was estimated by asking individuals the amount of time they would be willing to sacrifice to be in a better state of health when compared to the poorer state of health.

**Results/Conclusions:** Active surveillance with IMRT for progression was the strategy associated with the highest quality-adjusted life years (QALYs; 11.07). Brachytherapy and IMRT were less effective with QALYs of 10.57 and 10.51, respectively. Radical prostatectomy was the least effective strategy, with QALYs of 10.23. The difference between the most and least effective intervention was 4.1 months and 6 months between active surveillance and the most effective initial treatment (brachytherapy). In this study, 61% of those choosing active surveillance eventually underwent therapy, doing so at a median of 8.5 years after diagnosis. The risk of prostate cancer-specific death was 9% for initial treatment versus 11% for active surveillance.

**Reviewer's Comments:** In the United States only 16% to 40% of new diagnosed prostate cancer patients undergo surveillance, and the authors offer various barriers for choosing surveillance. To me, the financial interests of we physicians surely must play a role here. A recent article from the Wall Street Journal on the urolog centers brought some light to this concern. (Reviewer-Jonathan J. Beitler, MD, MBA).

Keywords: Surveillance, Low-Risk Prostate Cancer, Initial Treatment

Print Tag: Refer to original journal article
In patients with von Hippel-Lindau syndrome and adrenal pheochromocytoma, partial adrenalectomy should be performed rather than total adrenalectomy when it is technically feasible.

**Objective:** To assess the long-term outcome of partial adrenalectomy in patients with von Hippel-Lindau syndrome and adrenal pheochromocytoma.

**Design/Methods:** Patients with von Hippel-Lindau syndrome who were treated with partial adrenalectomy for pheochromocytoma were retrospectively reviewed. Oncologic and functional outcome data were determined.

**Results:** 36 partial adrenalectomies for pheochromocytoma were performed in 26 patients with von Hippel-Lindau syndrome. Twenty-three of the procedures were performed open and 13 were performed laparoscopically. At a mean follow-up of approximately 9 years, metastatic pheochromocytoma had not developed in any of the patients. Five local recurrences occurred in 3 patients and these were either treated with surgical removal or surveillance. Three of 26 patients (11%) subsequently developed pheochromocytoma in the contralateral adrenal gland and required partial adrenalectomy. Only 3 of 26 patients became steroid dependent.

**Conclusions:** The authors believe that partial adrenalectomy should be performed in patients with von Hippel-Lindau syndrome who have adrenal pheochromocytomas. They believe that, following partial adrenalectomy, local recurrence rates are low and the majority of patients can be spared steroid replacement.

**Reviewer’s Comments:** The authors have shown that, in patients with von Hippel-Lindau disease and adrenal pheochromocytomas, partial adrenalectomy rather than total adrenalectomy is the best option when it is technically feasible. Local recurrence only occurred in 3 of 26 patients and only 3 patients became steroid dependent. At a median follow-up of approximately 9 years, only 1 patient had died and that patient died of metastatic renal cell carcinoma. The authors do discuss the fact that patients who are diagnosed with pheochromocytoma at a young age and have a germline missense mutation of the von Hippel-Lindau gene may be at higher risk for tumor recurrence. In summary, partial adrenalectomy is a very viable option for patients who have von Hippel-Lindau syndrome and an adrenal pheochromocytoma. The recurrence rates are low and the risk of developing steroid dependency is also low. (Reviewer-George S. Benson, MD).

**Keywords:** Pheochromocytoma, von Hippel-Lindau Syndrome, Adrenalectomy

**Print Tag:** Refer to original journal article
Multifocal high grade prostatic intraepithelial neoplasia or bilateral disease is associated with an increased risk of prostate cancer.

**Objective:** To determine the relationship between high-grade prostatic intraepithelial neoplasia (HGPIN) on initial biopsy and a future diagnosis of prostate cancer.

**Participants/Methods:** Between December 1997 and February 2008, 328 men underwent a second prostate biopsy after being initially diagnosed with HGPIN. Another 335 men, who had no HGPIN seen on a first biopsy and who underwent a second biopsy, served as the controls. The need for a second biopsy was based on clinical suspicion only. HGPIN was also stratified into multifocal disease and bilateral disease. Kaplan-Meier analyses were used to estimate the subsequent rate of prostate cancer development.

**Results:** HGPIN, which was multifocal or bilateral, increased the hazard ratios of finding prostate cancer on subsequent prostate biopsy to 2.56 and 2.20, respectively.

**Conclusions:** The authors believe that multifocal HGPIN or bilateral disease significantly increases the risk of finding prostate cancer on subsequent biopsy.

**Reviewer's Comments:** The relationship of HGPIN and the subsequent diagnosis of carcinoma of the prostate on repeat biopsy continues to be controversial. The results of this study do show that multifocal disease and bilateral disease are risk factors for the subsequent diagnosis of prostate cancer. These authors recommend that when multifocal or bilateral HGPIN is found, a repeat biopsy should be performed within 2 to 3 years after the diagnosis to exclude the development of prostate cancer. Whether HGPIN progresses to carcinoma of the prostate or is just associated with carcinoma of the prostate is not clear. (Reviewer-George S. Benson, MD).

Keywords: Risk Factors, High Grade Prostatic Intraepithelial Neoplasia, Biopsy

Print Tag: Refer to original journal article
Objective: To describe the presenting prostate cancer characteristics in men treated in a public health system and to compare these characteristics to those of men whose diagnosis of prostate cancer is made in an academic or a community setting.

Participants/Methods: The records of 377 men diagnosed with prostate cancer in the San Francisco General Hospital System were reviewed. Their socio-demographic data and cancer characteristics were compared with information from the prostate cancer databases from CaPSURE™ and from the University of California-San Francisco tumor registry.

Results: The men attending the San Francisco General Hospital system were more likely to be nonwhite, insured under Medicaid, or uninsured than were men in the other 2 clinical settings. The men in the San Francisco General Hospital cohort had a higher incidence of adverse prostate cancer clinical characteristics, including median prostate specific antigen >10 ng/mL at diagnosis and a higher Gleason grade. Finally, the majority of patients in the San Francisco General Hospital cohort (67%) had intermediate- or high-risk disease based on the D'Amico classification system.

Conclusions: The authors believe that the men in the San Francisco General Hospital public health system presented with significantly worse disease than those who presented to an academic or community setting.

Reviewer's Comments: At face value, one could conclude that this study shows that access to quality care and socioeconomic factors that limit access to health care can have a significant negative role in cancer survival in men of different racial/ethnic backgrounds. Potentially, the lack of access to early detection programs and cancer screening may explain part of the disparity in prostate cancer presentation. On the other hand, several studies have shown that racial and ethnic disparities persist even after controlling for socioeconomic factors and access to medical care. The authors postulate that genetic factors may partially explain the findings. They also discuss dietary and environmental factors and discuss the effect on disease of a repeat stressor such as poverty. The results of this study show that men of lower socioeconomic status diagnosed with prostate cancer have a substantially higher burden of high-risk prostate cancer than men in a community setting and an academic center. Regardless of the cause, it is clear that efforts should be directed toward early diagnosis and management of prostate cancer in underserved patient populations. (Reviewer-George S. Benson, MD).