Docetaxel, doxorubicin, and cyclophosphamide adjuvant treatment of patients with high-risk, node-negative breast cancer improves 5-year disease-free survival by 4.8% at the cost of a 10% higher rate of grade 3 and 4 neutropenia.

Background: Better adjuvant treatment options are needed for axillary node-negative breast cancer patients to reduce their 25% recurrence rate after fluorouracil, doxorubicin, and cyclophosphamide (FAC) chemotherapy.

Objective: To evaluate the efficacy and safety of docetaxel, doxorubicin, and cyclophosphamide (TAC) in high-risk, node-negative breast cancer.

Design: Prospective, randomized, multinational trial.

Participants: 1060 operable node-negative breast cancer patients who were high risk due to ≥1 of the following: primary tumor >2 cm; negative estrogen and progesterone receptors; tumor grade 2 or 3, or age <35 years.

Methods: Patients were followed every 3 months for 2 years after treatment, every 6 months for 3 years, and then annually.

Interventions: Patients received 6, 3-week cycles of either TAC (docetaxel 75 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2) or FAC (fluorouracil 500 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2). All TAC patients received dexamethasone to prevent edema and ciprofloxacin 500 mg twice daily on days 5 to 14. Prophylactic granulocyte colony-stimulating factor (G-CSF) was given to TAC patients (after the first 230 randomizations) due to an initial >25% rate of febrile neutropenia.

Results: Compared with FAC, TAC reduced the event risk (relapse, new primary, or death) by 32% (18.2% vs 12.2%; HR, 0.68; P = 0.01). Five-year disease-free survival rates for TAC and FAC were 90.1% and 85.3% (HR, 0.67; P = 0.03), respectively. Overall survival was not significantly different (95.2% vs 93.5% at cutoff date; HR, 0.76; P = 0.29). The superiority of TAC was consistent across all subgroups. TAC produced significantly more grade 3 and 4 toxicity (28.2% vs 17.0%; P = 0.001), including more neutropenia (50.8% vs 39.5%; P < 0.001). Treatment was discontinued due to toxicity in 4.7% and 0.8% of TAC and FAC patients, respectively. One patient in each group developed congestive heart failure (grade 3) and acute leukemia. No patient died due to treatment.

Conclusions: Adjuvant TAC significantly improves disease-free survival for high-risk, node-negative breast cancer patients compared with FAC, thereby establishing a role for taxane-based adjuvant therapy in this population.

Reviewer’s Comments: These results confirm the feasibility of adjuvant taxane therapy in node-negative breast cancer, but whether taxanes will result in fewer overall relapses will require additional follow up. (Reviewer-Alan B. Grosbach, MD).

Keywords: Node-Negative/High-Risk Breast Cancer, Docetaxel, Adjuvant Chemotherapy, TAC, FAC
Objective: To determine the long-term outcomes from screening patients with BRCA1 and BRCA2 mutation carriers.

Design: Nonrandomized, prospective, multicenter study.

Participants/Methods: The Dutch MRI Screening Study (MRISC) enrolled women at 6 centers who had a genetic risk of breast cancer. Eligible patients were 25 to 75 years of age, with a cumulative lifetime risk of developing breast cancer of ≥15% due to familial or genetic predisposition. Women with symptoms or a personal history of breast cancer were excluded. The cohort was divided into 3 groups: mutation carrier (BRCA1, BRCA2, other mutation), high-risk non-mutation carrier (lifetime risk, 30% to 50%), and moderate-risk non-mutation carrier (lifetime risk, 15% to 30%). Participating women were screened with biannual clinical breast examination and annual mammography and MRI.

Results: The authors identified 2,157 eligible women. The mutation carrier group included 599 patients (BRCA1, n=422; BRCA2, n=172; PTEN/TP53, n=5), the high-risk group included 1,069 patients, and the moderate-risk group included 489 patients. A total of 97 cancers were detected in 94 patients; 80% were invasive and 20% were ductal carcinoma in situ (DCIS). Among the 97 cancers, 78 were detected by screening, 6 were identified at prophylactic mastectomy, and 13 were interval cancers not detected by screening. The overall detection rate was 10.4 per 1,000 woman-years at risk. The rate for BRCA2 mutation carriers was 39.2 per 1,000 and 26.3 per 1,000 for BRCA1 mutation carriers. The sensitivity for the screening methods was: clinical breast examination, 20.6%; mammography, 41.3%; and MRI, 70.7%. MRI was significantly more sensitive than mammography for invasive breast cancer, but less sensitive for DCIS. Among mutation carriers, the mammographic sensitivity was significantly less for BRCA1 as compared with BRCA2 carriers. Compared to BRCA2 carriers, BRCA1 carriers were younger, had a lower proportion of DCIS, had a higher proportion of interval cancers, had larger tumors, and had more estrogen receptor-negative tumors. Distant metastases occurred in 5 patients.

Conclusions: MRI is more sensitive than mammography and screening results were worse in BRCA1 mutation carriers.

Reviewer's Comments: The findings from this large prospective study are intriguing and suggest that patients with BRCA1 mutations should be screened more aggressively. (Reviewer-Todd M. Tuttle, MD).

Keywords: BRCA1, BRCA2, Breast Cancer, Screening

Print Tag: Refer to original journal article
Ambulatory cancer patients with risk scores ≥5 on a new assessment tool have a 6-month venous thromboembolism risk of 35%.

**Background:** Up to 20% of cancer patients experience venous thromboembolism (VTE), which is a major cause of morbidity and mortality. Identification of high VTE risk cancer patients would facilitate decisions on prophylactic management.

**Objective:** To test an expanded scoring system for VTE risk prediction in ambulatory cancer patients.

**Design:** Prospective, observational, cohort study.

**Participants:** 819 patients (363 females and 456 males) with newly diagnosed or progressive cancer (breast, lung, stomach, colorectal, pancreas, kidney, prostate, brain [high-grade glioma], lymphoma, myeloma) who had received no chemotherapy within 3 months and no radiation or surgery within 2 weeks were included.

**Methods:** Patients were observed for 2 years after baseline CBC, D-Dimer, and soluble P-selectin. Risk scores (Khorana, et al, J Clin Oncol 2009:27:4839-4847) were based on 2 points for a very-high-risk site of cancer (stomach, pancreas, brain), 1 point for a high-risk site (lung, kidney, lymphoma, myeloma), 0 for others, and 1 point each for platelet count ≥350,000, hemoglobin <10 g/dL and/or erythroid growth factor use, WBC >11,000; body mass index ≥35 kg/m2, plus 1 point each (expanded risk score) for soluble P-selectin ≥53.1 ng/mL, and D-Dimer ≥1.44 µg/mL.

**Results:** With median follow-up of 656 days, 61 patients (7.4%) had VTE (cumulative probability 6.0% at 6 months and 7.7% at 1 year). Four patients died of pulmonary embolism (PE) and 8 had incidental PE on CT scan. Patients with the highest Khorana risk scores (score ≥3; patients in this category = 93) had Kaplan-Meier VTE probability at 6 months of 17.7%, compared with 9.6% for a score of 2 (221 patients), 3.8% for score of 1 (229 patients), and 1.5% for a score of zero (276 patients). These differences were statistically significant (P <0.001). Each point increment approximately doubled the VTE risk (HR/point = 2.1), with no influence from age, sex, chemotherapy, surgery, or radiation. Compared to patients with a score of zero, those with scores of 1, 2, and 3 had HRs of 2.7, 5.5, and 9.5, respectively. Score sensitivity was 31.9% (probability of VTE in highest risk patients), specificity was 91.9% (probability of low risk in patients without VTE), positive predictive value was 22.1% (VTE probability in high-risk patients), and negative predictive value was 94.9% (probability of no VTE in low-risk patients). Using the expanded risk score (including P-selectin and D-Dimer), patients with scores ≥5 had a 35.0% VTE probability at 6 months compared with 20.3% in patients with score 4, 10.3% in patients with score 3, 3.5% for patients with score 2, 4.4% for score 1, and 1.0% for zero. The linear trend in risk was statistically significant (P <0.001), and univariate and multivariate analyses demonstrated incremental HR/risk score point of 1.8 and 1.9.

**Conclusions:** Inclusion of soluble P-selectin and D-Dimer improve the accuracy of VTE risk assessment in cancer patients.

**Reviewer’s Comments:** Use of this scoring system permits identification of patients who may be candidates for primary VTE prophylaxis, such as brain tumor patients. (Reviewer-Alan B. Grosbach, MD).

Keywords: Venous Thromboembolism, Cancer Patients, Prediction, D-Dimer, P-Selectin

Print Tag: Refer to original journal article
Peripheral neuropathy limits cumulative bortezomib to approximately 50% of the planned dose in most myeloma patients treated on a twice-weekly schedule.

**Background:** Bortezomib, a novel agent for multiple myeloma treatment, is dose-limited by neurotoxicity when given twice-weekly.

**Objective:** To determine the impact of once- versus twice-weekly bortezomib combination therapy for multiple myeloma.

**Design:** Retrospective analysis of Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) phase 3 bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) trial.

**Participants:** 511 newly diagnosed myeloma patients, ineligible for stem cell transplant, who received either once- (n=372) or twice-weekly (n=139) bortezomib.

**Methods:** Bortezomib doses were given weekly instead of twice-weekly after the first 139 patients were enrolled.

**Interventions:** Initially, nine 6-week cycles of bortezomib 1.3 mg/m² were given (cycles 1 to 4: days 1, 4, 8, 11, 22, 25, 29, and 32; cycles 5 to 9: days 1, 8, 22, and 29), and subsequently, nine 5-week cycles 1.3 mg/m² (days 1, 8, 15, and 22) were given. All patients received melphalan 9 mg/m² + prednisone 60 mg/m² (days 1 to 4) for each of the 9 cycles. Thalidomide 50 mg/day was given to VMPT-VT patients during the 9 induction cycles and for 2 years of maintenance. Bortezomib maintenance dose (VT) was 1.3 mg/m² every 2 weeks.

**Results:** Median follow-up was 23.2 months. There were no statistically significant differences in median progression-free survival (PFS), 3-year PFS, 3-year time-to-next-therapy, or 3-year overall survival between patients receiving once- versus twice-weekly bortezomib for either VMPT-VT or VMP patients. Complete (CR), very good partial response (VGPR), and partial response (PR) rates, as well as time to response and response duration, were also not statistically different. Overall, 85% (once-weekly) and 86% (twice-weekly) of patients had partial or better responses (30% and 35% CRs). Median cumulative bortezomib doses were similar (39.4 mg/m² for once weekly and 40.1 mg/m² for twice weekly) with 39% of once-weekly and 13% of twice-weekly patients receiving >90% of planned bortezomib dose. Thrombocytopenia was the only grade 3/4 hematologic toxicity that differed between once- and twice-weekly patients (19% vs 26%; \( P = 0.08 \)), but once-weekly patients had significantly less grade 3/4 neuropathy (8% vs 28%; \( P < 0.001 \)), sensory neuropathy (3% vs 16%; \( P < 0.001 \)), and sensory neuropathy plus neuralgia (3% vs 8%; \( P = 0.01 \)). The development of grade 3/4 neuropathy occurred almost exclusively during induction therapy. Peripheral neuropathy required dose reductions in 41% of twice-weekly versus 17% of once-weekly patients (\( P < 0.001 \)), and prevented treatment completion in 3 times as many twice-weekly patients (15% vs 5%; \( P < 0.01 \)). Similarly significant discontinuation rates were observed among patients who did not receive thalidomide (16% vs 4%; \( P = 0.002 \)). Thalidomide increased the overall incidence of neuropathy (HR, 1.32; \( P = 0.029 \)), but not that of grade 3/4 neuropathy (HR, 1.24; \( P = 0.41 \)). Nearly two-thirds of all patients had neuropathy improvement that occurred approximately 1 month sooner in the once-weekly patients.

**Conclusions:** Once-weekly bortezomib produces less neuropathy with no reduction in effectiveness.

**Reviewer’s Comments:** The nearly identical median cumulative bortezomib doses in both groups support once-weekly dosing at least after a few weeks of induction. (Reviewer-Alan B. Grosbach, MD).
Keywords: Multiple Myeloma, Bortezomib, Once-Weekly Treatment, Efficacy, Safety

Print Tag: Refer to original journal article
There are significant improvements in overall survival and progression-free survival among patients who receive consolidation radiation therapy after R-CHOP for diffuse large B-cell lymphomas.

**Background:** Diffuse large B-cell lymphoma (DLBCL) is an aggressive and common non-Hodgkin’s lymphoma (NHL), composing 30% to 40% of NHL in adults. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard of care for DLBCL. Four randomized trials (Southwest Oncology Group 8736, Groupe d’Etudes des Lymphomes de l’Adulte LNH 93-1, Eastern Cooperative Oncology Group 1484, and the GELA LNH 93-4) have not supported the use of radiation for DLBCL. However, all 4 focused on stage I/II patients and predated rituximab. Aviles, however, did publish a pre-rituximab prospective study showing that for patients with bulky stage IV aggressive lymphomas who had a complete response to chemotherapy, the addition of consolidative radiation therapy (RT) increased 5-year survival from 66% to 87% ($P=0.01$).

**Objective:** To clarify the role of RT in patients with DLCBL who are treated with R-CHOP.

**Design:** Retrospective review from M.D. Anderson.

**Participants/Methods:** 469 patients treated at M.D. Anderson between 2001 and 2007 were analyzed. Median age was 61 years, and 20% were stage I, 20.5% were stage II, 16.4% were stage III, and 43.1% had stage IV disease. Bulky disease (ie, any mass >5 cms) was present in 37%. Complete remission (CR) was obtained in 68% to 79% of stage I to IV patients. RT was delivered to 96 of the 347 patients who achieved a CR by both positron emission tomography (PET) and CT scan. Approximately 84% of the patients were given R-CHOP and 30.2% received RT. On univariate analysis, the following factors were significant for overall survival (OS) and progression-free survival (PFS): stage III/IV disease at presentation; type and number of cycles of chemotherapy; administration of RT; international prognostic index (IPI) score; response to chemotherapy; and the presence or absence of the 3 adverse factors (triple negative, triple positive; ie high Ki67, high PET SUV, and bulky disease). Using only the patients who received 6 to 8 cycles of R-CHOP, the factors were significant again. A third univariate analysis was performed for the 291 patients who received 6 to 8 cycles of R-CHOP and had a documented CR. Once again, stage, triple negative versus triple positive, IPI score, and RT were prognostically significant. Multivariate analysis in this subgroup of patients who achieved CR after 6 to 8 cycles of R-CHOP, demonstrated that OS and PFS were significantly associated with RT and triple negative/triple positive. Matched-pair analysis was performed on 44 matched pairs of stage I and II patients who received 6 to 8 cycles of R-CHOP, and, once again, patients who received RT had longer OS (HR, 0.52) and PFS (HR, 0.45). A similar matched-pair analysis of 30 pairs was performed in stage III and IV patients who received 6 to 8 cycles of R-CHOP; RT was again associated with significantly better OS and PFS. Local control was 100% in the patients who received involved field RT.

**Conclusions:** Significant improvements in OS and PFS were seen among patients who received consolidation RT after R-CHOP for DLBCL.

**Reviewer’s Comments:** What is most impressive to me is that all of these patients had complete responses; and, in multiple ways of looking at the data, radiation improved both PFS and OS. (Reviewer-Jonathan J. Beitler, MD, MBA).

**Keywords:** Diffuse Large B-Cell Lymphoma, Consolidative Radiation Therapy, R-CHOP
HCV+ Patients With DLBCL at Increased Risk of Severe Hepatotoxicity During R-CHOP

Hepatic Toxicity and Prognosis in Hepatitis C Virus–Infected Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab-Containing Chemotherapy Regimens: A Japanese Multicenter Analysis.

Ennishi D, Maeda Y, et al:

Blood 2010; 116 (December 9): 5119-5125

Hepatitis C virus infection places diffuse large B-cell lymphoma patients at markedly increased risk of severe hepatotoxicity during R-CHOP chemotherapy, but overall prognosis appears not to be adversely affected in a case-control study.

Background: Reports of outcomes in patients with diffuse large B-cell lymphoma (DLBCL) and hepatitis C virus (HCV) infection are limited, and mostly predate the routine use of rituximab.

Objective: To determine prognosis and hepatic toxicity for DLBCL patients receiving rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Design: Multicenter, retrospective, case-control study.

Participants: 131 HCV-positive patients and 454 contemporaneously treated HCV-negative patients who received R-CHOP for DLBCL.

Methods: Anti-HCV antibodies defined HCV infection. Severe hepatotoxicity (grade 3 or 4) was defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal.

Results: 57 of the HCV-positive patients (43%) had chronic hepatitis (CH) when DLBCL was diagnosed, and 20 (15%) had hepatic cirrhosis. With median follow-up of 31 months (HCV+ patients) and 32 months (HCV-patients), complete remission rates in the 2 groups were nearly identical (81% and 83%), and 3-year progression-free survival (PFS) was not significantly different (69% vs 77%; P =0.22). Three-year overall survival (OS) was marginally superior in HVC- patients (84% vs 75%; P =0.07). There was no correlation between HCV infection (positive vs negative) and lymphoma-specific survival (3-year, 84% vs 86%; P =0.80). HCV+ patients had a 27% rate of severe hepatic toxicity compared with 3% for HCV- patients, with HCV positivity identified as a significant risk factor for severe toxicity on multivariate analysis (HR, 14.72; P <0.001). Among HCV+ patients, baseline transaminase elevation was the only factor predictive of severe hepatotoxicity on multivariate analysis. Sixteen patients required treatment modification due to hepatic toxicity, but HCV positivity was not associated with poor PFS or OS. Six of 24 deaths among HCV+ patients were due to liver failure (14 due to DLBCL progression and 4 to other causes). Among 34 patients with HCV-RNA levels available, pre- and post-treatment, and at peak during treatment mean levels rose and fell significantly from 1001 to 3187 (P for increase 0.006) then to 1986 (P =0.003). The improvement occurred without antiviral treatment.

Conclusions: HCV+ patients with DLBCL are at increased risk of severe hepatotoxicity during R-CHOP treatment necessitating careful liver function monitoring.

Reviewer’s Comments: Rituximab treatment for DLBCL carries substantial risk in patients with HCV, but the risk appears to be worth taking since lymphoma control remains the life-limiting factor. Careful monitoring of liver function tests is mandatory during treatment. (Reviewer- Alan B. Grosbach, MD).

Keywords: Diffuse Large B-Cell Lymphoma, Rituximab, R-CHOP, Hepatotoxicity, Hepatitis C Virus

Print Tag: Refer to original journal article
Background: Despite the dramatic impact imatinib has had on chronic myelogenous leukemia (CML) outcomes, most patients do not achieve complete molecular remission.

Objective: To demonstrate whether higher imatinib doses or imatinib combinations produce higher molecular response rates in CML than standard dose imatinib.

Design: Phase 3, prospective, randomized, multicenter trial.

Participants: 636 newly-diagnosed, untreated patients with chronic phase BCR-ABL-positive CML.

Methods: Major and superior molecular responses were defined as $4 \log_{10}$ and $3 \log_{10}$ reductions in $BCR-ABL$ transcripts from standardized baseline level. After an initial 2-weeks of imatinib 400 mg/day, patients were randomized to imatinib 400 mg/day (I400), imatinib 600 mg/day (I600), imatinib 400 mg/day + 90 µg/week peginterferon alfa-2a (I+peg), or imatinib 400 mg/day + 20 mg/m² cytarabine/day on days 15 through 28 of each 28-day cycle (I+araC).

Results: Rates of complete hematologic response at 3 months were virtually identical in all groups (89% to 95%; $P > 0.05$). The 6-month complete cytogenetic response rate was highest in the I600 group (69%) compared with 59% (I+araC), 57% (I+peg), and 50% (I400) ($P = 0.005$), but by 12 months, there was no significant difference between groups (58% to 70%; $P > 0.05$). I+peg produced the highest rate of major molecular response at 12, 18, and 24 months at 57% ($P < 0.001$), 62% ($P = 0.004$), and 64% ($P = 0.006$), respectively, and the highest rates of superior molecular response (30% ($P = 0.001$), 35% ($P = 0.002$), and 38% ($P = 0.001$), respectively, and undetectable residual disease at 24 months 16% ($P = 0.01$). The impressive results from I+peg were tempered by toxicity. Forty-five percent of I+peg patients stopped peginterferon during the first year of treatment (versus 38% of the I+araC group and 7% and 8% in the interferon-only groups). The median duration of peginterferon treatment was 12 months for all patients in the group and 8 months for those who discontinued the drug. I+peg patients had the highest rates of grade 3 and 4 rash (8%), edema (3%), and neutropenia (49%). Depression (all grades) was observed in 7% of I+peg and 8% of I+araC patients. I+peg patients who took peginterferon for <4 months had rates of major and superior molecular response and undetectable residual disease that were similar to those for I400 patients. Only 18 patients progressed to the accelerated phase or blast crisis (I400, 4; I600, 5; I+araC, 4; and I+peg, 5).

Conclusions: Imatinib plus peginterferon produces higher rates of molecular response than imatinib alone, but toxicity limits the usefulness of peginterferon.

Reviewer's Comments: This study fails to demonstrate a clear advantage for treatments other than single-agent imatinib for most patients with chronic myelogenous leukemia. (Reviewer-Alan B. Grosbach, MD.)

Keywords: Chronic Myelogenous Leukemia, Imatinib, Peginterferon, Cytarabine

Print Tag: Refer to original journal article
Pancreatic cancer has subclones within the index cancer that are geographically distinct within the primary lesion.

**Background:** As all our listeners and readers know, pancreatic cancer is a deadly disease, and through the decades, we have made scant progress. The findings of this selection from the basic science journal *Nature*, may jolt our understanding of pancreatic cancer.

**Objective:** To understand the natural history of pancreatic cancer.

**Design:** Autopsy study of 7 individuals with end-stage pancreatic cancer.

**Participants:** Each of these 7 patients had metastatic foci in ≥2 anatomic sites. Metastatic sites were most often the liver, lung, and peritoneum.

**Methods:** Cell lines were created from one of the metastases present in each patient. These cells were compared to an earlier study of 24 pancreatic patients who had 426 somatic mutations in 388 different genes. For each somatic mutation detected in the 7 index metastatic sites, it was determined whether the same mutations existed in an anatomically separate metastatic site and in the primary tumor from whence the metastases originated. Two categories of mutations were defined. "Founder" mutations were mutations found in all 3 samples from the same patient. All other mutations were characterized as "Progressor" mutations. Evolutionary maps were constructed for each patient's cancer based on the somatic mutations, allelic losses, and the location of individual metastatic deposits. To distinguish whether the Progressor mutations occurred in the metastatic site or in the pancreas, the primary tumor from 2 patients was sectioned into numerous 3-dimensionally organized pieces.

**Results:** 64% of the somatic mutations were Founder mutations, common to all 3 sites sampled. This means that the majority of the mutations were acquired before the development of metastases. Analysis of the primary tumor in 3 dimensions found the subclone Progressor mutations were present in the primary tumor in different locations. Subclone mutations were not randomly located within the primary, but were localized to areas of the primary cancer. The primary cancer was heterogeneous, not just the metastases. Using Ki-67 labeling, a mathematical model was employed to find that there was an average of 11.7 years from initiation of tumorigenesis until birth of a cell that gave rise to the Founder mutations. From that point, there was an average of 6.8 years until the birth of a cell giving rise to the index lesion, and an average of 2.7 years until the patient's death.

**Conclusions:** Primary pancreatic cancer contains a mix of geographically distinct subclones that are present within the primary tumor years before they metastasize.

**Reviewer’s Comments:** What I believe from the article is that there are geographically distinct subclones within the body of the index pancreatic cancer. I am not sold on the very long gestational periods that these authors describe. (Reviewer-Jonathan J. Beitler, MD, MBA).

Keywords: Pancreatic Cancer, Distant Metastasis, Genetics, Tumor Heterogeniety

Print Tag: Refer to original journal article
Liver-Directed Surgery Can Lead to Long-Term Survival

Surgical Management of Hepatic Neuroendocrine Tumor Metastasis: Results From an International Multi-Institutional Analysis.

Mayo SC, de Jong MC, et al:

Ann Surg Oncol 2010; 17 (December): 3129-3136

Nearly all patients develop tumor recurrence after surgical treatment of liver metastases from neuroendocrine tumors.

Objective: To determine the efficacy of surgical management of hepatic metastases from neuroendocrine tumors.

Design: Retrospective multicenter study.

Participants/Methods: The authors included patients who underwent surgical treatment for hepatic metastasis for neuroendocrine tumors at 8 major centers. Liver-directed treatment included resection, ablation, or combined resection plus ablation. Overall survival time was calculated from date of surgery to last follow-up.

Results: The authors identified 339 patients. The most common histology was carcinoid tumor; most tumors were low grade. Most patients had symptoms related to the primary tumor. The majority of patients (83%) had isolated liver metastases. With a median follow-up of 43 months, 58.7% had recurred. The 1-, 3-, and 5-year disease-free survival rates were 56.9%, 24.2%, and 5.9%, respectively. The most common site of first recurrence was the liver. Median time to recurrence was 15.2 months. The 5- and 10-year recurrence rates were 94% and 99%, respectively. The median survival after the initial liver surgery was 125 months, with a 10-year survival rate of 51%. On multivariate analysis, nonfunctional neuroendocrine tumors, synchronous presentation of liver metastases, and concomitant extrahepatic disease were significant predictors of poor outcome.

Conclusions: Surgical management of hepatic metastases from neuroendocrine tumors can lead to long-term survival in many patients.

Reviewer’s Comments: Recent improvements (somatostatin, hepatic artery embolization) in the nonsurgical treatment of hepatic metastases from neuroendocrine tumors have brought into question the role of surgical treatment. In this study, nearly all patients developed tumor recurrence after surgery, yet many still lived for long periods of time. These findings suggest little efficacy for surgical treatment for this disease. (Reviewer-Todd M. Tuttle, MD).

Keywords: Hepatic Neuroendocrine Tumor, Metastasis, Surgical Management

Print Tag: Refer to original journal article
Patients treated with trimodality therapy found no benefit with PET complete response, likely because FDG-PET residual disease was resected.

**Background:** Survival for esophageal cancer is still unacceptable and there has been no improvement in survival for the past 20 years. According to these authors, trimodality therapy has been favored over surgery alone in the literature. They also cite 2 studies demonstrating no advantage to adding surgery to definitive chemoradiation for squamous cell cancers. Survival rates for chemoradiation were 25% to 40%, similar to survival rates for trimodality care. Given the uncertain benefit of surgery and the high complication rate of surgery following chemoradiation, balanced against the high local failure rate after chemoradiation alone, there is great interest in a tool that can predict who can forego surgery after chemoradiation.

**Objective:** To delineate the role of FDG-PET after chemoradiation in predicting who will need esophageal resection.

**Design:** Retrospective review.

**Methods:** Radiation therapy was 50.4 Gy and concurrent chemotherapy was 5FU and Cisplatin in 90% of patients. Of 163 patients (54%), 88 received trimodality therapy and 75 received chemoradiation alone. Reasons for not resecting included: medically inoperable status, unresectable or metastatic disease, and patient refusal. Post-chemoradiation FDG-PET scanning was obtained in only 31% of the 105 patients potentially available for scanning. Pretreatment and post-treatment FDG-PET scanning was performed prior to chemoradiation and after chemoradiation, but prior to resection. FDG-PET complete response was defined as an SUV of ≤3.

**Results:** Patients treated with chemoradiation alone had significantly worse prognostic factors. An FDG-PET complete response predicted a better median survival (29.7 vs 15.9 months). For patients treated with chemoradiation alone, achieving a FDG-PET complete response improved the 2-year survival to 71% versus 11% if there was less than a FDG-PET complete response. Local freedom from failure at 2 years was also significantly better for the FDG-PET complete responders (75% vs 28%). There were fewer adenocarcinomas among those achieving a FDG-PET complete response (37% vs 71%). In patients who had trimodality therapy, those with FDG-PET complete response were more likely to have a significant pathologic response, which meant either pathologic complete response or only microscopic residual disease was questionable viability (53% vs only 33% probability of a significant pathologic response if less than a FDG-PET complete response).

**Conclusions:** FDG-PET may identify 2 groups of patients who will not benefit from surgery after chemoradiation. One in 6 patients developed metastatic or unresectable disease. Those who achieved a complete FDG-PET response to chemoradiation had survival and local control rates that were the same as those having surgery, despite worse baseline characteristics.

**Reviewer's Comments:** This is an interesting hypothesis that needs to be tested prospectively. Another take-home point is the reduced FDG-PET complete response rate for the adenocarcinomas. I am also unclear as to when, after the chemoradiation, to obtain the FDG-PET. (Reviewer-Jonathan J. Beitler, MD, MBA).

Keywords: Esophageal Cancer, Survival, FDG-PET, Esophageal Resection

Print Tag: Refer to original journal article
Does Risk of Cancer Decrease After Obesity Surgery?

Risk of Obesity-Related Cancer After Obesity Surgery in a Population-Based Cohort Study.
Ostlund MP, Lu Y, Lagergren J:

Ann Surg 2010; 252 (December): 972-976

This study found that there is no overall decreased risk of obesity-related cancer after obesity surgery.

**Objective:** To determine if the risk of obesity-related cancer decreases with time after obesity surgery.

**Design:** Population-based database.

**Participants/Methods:** The authors used a population-based cohort of patients who were aged >18 years and had undergone obesity surgery as registered in the Swedish Patient Register from 1980 through 2007. The risk of developing obesity-related cancer among the surgery cohort was compared with the expected baseline risk in the Swedish population of corresponding age, gender, and calendar year. The obesity-related cancers included breast, prostate, colorectal, endometrial, ovarian, renal, esophagus, liver, pancreas, gallbladder, non-Hodgkins lymphoma, leukemia, and thyroid.

**Results:** The cohort included 13,123 patients and 125,049 person-years of follow-up. The mean follow-up time was 9 years. The authors identified 296 new obesity-related cancers. Most obesity operations were restrictive, which included either vertical banding gastroplasty or gastric banding. There was no overall decreased risk of obesity-related cancer (standardized incidence ratio [SIR], 1.04; 95% CI, 0.93 to 1.17); however, males were at a slightly increased risk (SIR, 1.41; 95% CI, 1.09 to 1.81). No significant risk reduction of obesity-related cancer was identified with increased follow-up time. The risk of breast cancer was significantly reduced after obesity surgery. There was no reduction in the risk of prostate cancer. The risk of colorectal cancer, endometrial cancer, and renal cancer were significantly increased after obesity surgery. The risk of developing any cancer was not significantly decreased after obesity surgery.

**Conclusions:** The long-term risk of obesity-related cancer might not decrease after weight loss from obesity surgery.

**Reviewer’s Comments:** This is an interesting study but has 2 important limitations acknowledged by the authors: lack of data on individual weight loss and lack of information on body mass index in the baseline population. (Reviewer-Todd M. Tuttle, MD).

Keywords: Obesity-Related Cancer, Risk, Obesity Surgery

Print Tag: Refer to original journal article
Survivors Who Participate in Clinical Trials Have Improved Preventive Health Care

Routine Preventive Care and Cancer Surveillance in Long-Term Survivors of Colorectal Cancer: Results From National Surgical Adjuvant Breast and Bowel Project Protocol LTS-01.


J Clin Oncol 2010; 28 (December 20): 5274-5279

In this study, high rates of cancer surveillance were achieved among colorectal cancer survivors who had participated in clinical trials.

Objective: To evaluate routine preventive care and cancer surveillance in long-term colorectal cancer survivors.

Design: Prospective multicenter study.

Participants/Methods: The Long-Term Survivors Study invited 60 National Surgical Adjuvant Breast and Bowel Project study sites that had previously participated in colon and rectal cancer adjuvant treatment trials. Patients who had participated in these protocols and were long-term survivors (≥5 years) were identified and asked to participate. Telephone interviews were conducted. A case-matched cohort (3:1; matched on age, gender, race, and education) was obtained from the National Health Interview Survey. The survey was developed to investigate health behaviors and quality of life of long-term survivors.

Results: The authors successfully recruited 708 long-term survivors and 2124 matched controls who completed the interview. Most patients were white (93%) with a mean age of 66 years. The median survival from diagnosis was 8 years. Long-term survivors were more likely to have a usual source of health care compared to controls (98% vs 94%). Long-term survivors were more likely to have received a flu shot in the previous 12 months as compared with controls. Significantly more women in the survivor group had a Pap smear or mammogram in the previous 12 months than in the control cohort. Among men, significantly more patients had a prostate-specific antigen test within the previous 12 months as compared with the control group. Among the survivors, 97% of patients had a colonoscopy within the previous 5 years and 74% within the previous 2 years. Also among survivors, carcinoembryonic antigen testing and CT scan were performed within 5 years in 88% and 66% of patients, respectively.

Conclusions: The authors demonstrated the feasibility of utilizing clinical trials to identify, study, and contact long-term cancer survivors and comparing them with the general population.

Reviewer's Comments: The authors conclude that long-term colorectal cancer survivors who participated in clinical trials practiced improved preventive health care and cancer screening as compared to the general population. (Reviewer-Todd M. Tuttle, MD).

Keywords: Colorectal Cancer Survivors, Preventive Care, Surveillance

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Robotic Thyroidectomy Using Bilateral Axillo-Breast Approach Safe, Effective

Outcomes of 109 Patients With Papillary Thyroid Carcinoma Who Underwent Robotic Total Thyroidectomy With Central Node Dissection Via the Bilateral Axillo-Breast Approach.

Lee KE, Koo DH, et al:

Surgery 2010; 148 (December): 1207-1213

Robotic thyroidectomy appears to be an effective operation for papillary thyroid cancer given the low thyroglobulin levels after surgery.

Objective: To evaluate the immediate and 1-year outcomes after endoscopic thyroidectomy for papillary thyroid carcinoma.

Design: Prospective single-center study.

Participants/Methods: The authors included 109 patients who underwent robotic thyroidectomy using the bilateral axillo-breast approach at a single center. The thyroidectomy and central neck dissection were performed through bilateral ports placed into the axilla. Clinicopathologic characteristics were recorded. Permanent recurrent laryngeal nerve palsy and hypoparathyroidism were evaluated at 1 year.

Results: The mean patient age was 39 years. The mean tumor size was 0.69 cm. Bilateral disease was present in 15% of patients. The mean number of retrieved lymph nodes was 2.5. The mean operation time was 206 minutes. One patient developed immediate postoperative bleeding. One patient developed chylous drainage. No patient was converted to an open operation. No wound infections were observed. Transient recurrent laryngeal nerve palsy and hypocalcemia occurred in 16% and 19% of cases, respectively. At 1 year, there was 1 case of permanent recurrent laryngeal nerve palsy and 2 cases of hypoparathyroidism. Radioactive iodine was administered to 52% of patients; among these patients, the mean stimulated thyroglobulin level was 1.84 ng/mL and 76% had stimulated levels <1.0 ng/mL.

Conclusions: Robotic thyroidectomy using the bilateral axillo-breast approach is safe and effective. The authors suggest that this technique may be suitable for low-risk patients with papillary thyroid cancer.

Reviewer's Comments: The authors report encouraging early results with this surgery. Clearly, the advantage of this approach is the absence of any visible incision on the neck, which is an important concern for many young patients. Nevertheless, the operative time was quite long as compared to conventional thyroidectomy. Also, the number of retrieved lymph nodes from the central neck dissection seems low. (Reviewer-Todd M. Tuttle, MD).

Keywords: Endoscopic Thyroidectomy, Papillary Thyroid Carcinoma, Outcomes

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Dose-Volume Constraints Associated With Preserved Long-Term Swallowing Function

Candidate Dosimetric Predictors of Long-Term Swallowing Dysfunction After Oropharyngeal Intensity-Modulated Radiotherapy.

Schwartz DL, Hutcheson K, et al:

Int J Radiat Oncol Biol Phys 2010; 78 (December 1): 1356-1365

In the context of glottic sparing, anterior oral cavity and superior pharyngeal constrictor dose constraints may predict for long-term dysphagia.

Background: In my world of head and neck radiation oncology, everyone is measuring dosage to various critical normal organs and advising us to avoid irradiating normal structures. Dr Eisbruch has suggested that the superior constrictors and the supraglottic laryngeal structures are key to maintaining swallowing. On the other hand, it is hard to bypass the laws of physics.

Objective: To investigate long-term swallowing function in patients undergoing intensity-modulated radiotherapy (IMRT) irradiation for oropharyngeal cancers and focusing on patients with at least 12 months of follow-up.

Design: Prospective study from M.D. Anderson Cancer Center.

Participants/Methods: 48 patients with head and neck cancer were prospectively enrolled in an institutional Phase II chemoradiation trial. Swallowing outcomes were prospectively collected. Dosimetry was retrospectively correlated with swallowing outcomes in 31 patients with base of tongue or tonsillar cancers. Doses were delivered in 30 to 33 daily fractions: CTV1, 66 to 70 Gy; CTV2, 60 to 63 Gy; and CTV3, 54 to 57 Gy. In all cases, IMRT was matched at the superior aspect of the arytenoid with a conventional anterior-posterior bilateral supraclavicular field using a 3 x 3 cm larynx block and treating to 50 Gy in 25 fractions. The larynx block was subsequently extended to the lower border of the supraclavicular field to shield the spine after 40 to 42 Gy. Boosts to low neck nodes with gross disease or adjacent to gross disease were used as needed. Routine dose-limiting structures were parotids, spinal cord, brainstem, mandible, and glottis. Additional structures were contoured retrospectively: submandibular glands, oral cavity (anterior vs posterior), and pharyngeal constrictors (superior, middle, and inferior based on cranial and caudad surfaces of the hyoid bone). Aspiration was graded using the Penetration–Aspiration scale with ≥6 considered aspiration. Oropharyngeal Swallowing Efficiency (OPSE) was evaluated by modified barium swallow and analyzed by 4 trained clinicians who were blinded to the patient's identity. Post-RT OPSE values were normalized to baseline values.

Results: Post-treatment OPSE were performed, on average, at 6.6, 12.7, and 24.5 months post-treatment. Mean OPSE scores were 13.2 points lower than baseline at 6 months without significant improvement thereafter. On univariate analysis, tonsil patients had worse function than base-of-tongue cancer patients. There were 2 constraints that were independently predictive for long-term dysphagia problems, V30 >65% for anterior oral cavity and V55 >80% for superior pharyngeal constrictors.

Conclusions: In the context of glottic sparing, anterior oral cavity and superior pharyngeal constrictor dose constraints may predict for long-term dysphagia. These theories are undergoing prospective validation.

Reviewer's Comments: The importance of the superior constrictors has been identified by Eisbruch and Levendag's groups. One wonders how the supraclavicular matching technique from M.D. Anderson is reflected in the unintended irradiation of the oral cavity. (Reviewer-Jonathan J. Beitler, MD, MBA).

Keywords: Constraints, Dysphagia, IMRT

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Management of Rectal Injury During Radical Prostatectomy

Critical Appraisal of Management of Rectal Injury During Radical Prostatectomy.

Roberts WB, Tseng K, et al:

Urology 2010; 76 (November): 1088-1091

Rectal injuries that are recognized intraoperatively at the time of radical prostatectomy can be primarily repaired without the need for a diverting colostomy.

Objective: To describe the incidence and management of rectal injuries occurring during radical prostatectomy for prostate cancer.

Participants/Methods: 11,452 men who underwent radical prostatectomy for prostate cancer were retrospectively reviewed. The management and outcome of patients who experienced rectal injury are described.

Results: Out of 11,452 men who underwent radical prostatectomy for prostate cancer, approximately 10,000 underwent radical retropubic prostatectomy and approximately 1300 underwent laparoscopic retropubic prostatectomy with or without robotic assistance. Rectal injury occurred in 18 men. Twelve injuries occurred in the radical retropubic prostatectomy group and 6 in the laparoscopic group. Sixteen of 18 injuries were recognized intraoperatively and were primarily repaired without a diverting colostomy. In 4 of the cases, a pedicle of omentum was used as an interposing layer. Two of 16 patients who underwent primary repair developed a rectourethral fistula. In neither of these cases was a pedicle of omentum used. The 2 rectal injuries that were not recognized intraoperatively were treated with conservative management initially but ultimately required repair of the fistula with a transrectal advancement flap.

Conclusions: The authors report that rectal injury is infrequently seen during radical prostatectomy and they believe that when a rectal injury is recognized intraoperatively, it should be primarily repaired. Following primary repair of the injury, rectourethral fistula is prevented in approximately 88% of men. In patients with unrecognized rectal injury who subsequently present with a rectourethral fistula, conservative management tends to fail and these patients eventually require delayed surgical repair.

Reviewer's Comments: This is a good paper that presents impressive data showing that the majority of rectal injuries seen intraoperatively at the time of radical prostatectomy for prostate cancer can be primarily repaired without the need for a diverting colostomy. The incidence of rectal injury in this large series is low. Rectal injuries occurred in 0.12% of men undergoing radical retropubic prostatectomy and in 0.47% of men undergoing laparoscopic radical prostatectomy. Primary repair prevented the subsequent occurrence of a rectourethral fistula in 88% of men. None of the men who underwent primary repair and had omental interposition performed developed a fistula. Although it does make sense to attempt to perform a tissue interposition during primary repair, use of omentum can be difficult in patients who have undergone prior upper abdominal surgery and can be difficult to perform through a lower midline incision. Of note is the fact that all of the rectal injuries that occurred in this series occurred in nonirradiated patients. (Reviewer-George S. Benson, MD).

Keywords: Radical Prostatectomy, Rectal Injury, Primary Repair of Rectal Injury

Print Tag: Refer to original journal article
In patients who present with renal cell carcinoma, the proportion of patients presenting with small, asymptomatic lesions that are amendable to partial nephrectomy continues to increase.

**Objective:** To describe the contemporary clinical epidemiology of renal cell carcinoma.

**Design:** A population-based case-control study in Detroit and Chicago was performed by the National Cancer Institute.

**Participants/Methods:** 1136 patients who had renal cell carcinoma and consented to an interview and medical record review were evaluated. The trends in clinical presentation and treatment of the renal cell carcinoma in this series conducted from 2002 through 2007 are described.

**Results:** 52% of patients had tumors ≤4 cm in diameter. The proportion of patients who were asymptomatic increased from 35% in 2002 to 50% in 2007. Hypertension and diabetes were common comorbidities in these patients and 24% of patients had at least 2 significant comorbidities at the time of cancer diagnosis. Importantly, <20% of patients underwent nephron sparing surgery.

**Conclusions:** The authors believe that the number of patients with renal cell carcinoma who present with small, asymptomatic lesions continues to increase. Despite general consensus that many of these lesions should be treated with nephron sparing surgery, most of the cases in this series were still treated with radical nephrectomy.

**Reviewer's Comments:** This paper provides good documentation of what many physicians think they already know. Specifically, the proportion of patients with renal cell carcinoma who have localized, asymptomatic, small tumors continues to increase. From 2002 until 2007, the proportion of asymptomatic cases increased from 35% to 50%. Many of these patients with small renal cell carcinomas have significant comorbidities and 24% of patients in this series had at least 2 significant comorbid conditions at the time of diagnosis of their renal cell carcinoma. Despite the data showing that many of these patients survive longer with partial nephrectomy than with radical nephrectomy, the majority of patients in this 5-year study underwent radical nephrectomy rather than partial nephrectomy. Hopefully, this trend will reverse in the near future. (Reviewer-George S. Benson, MD).

**Keywords:** Renal Cell Carcinoma, Radical Nephrectomy, Partial Nephrectomy
The use of statins may lower serum prostate-specific antigen levels, but the effect is small and the clinical importance is limited.

**Objective:** To determine the effect of statins on serum prostate-specific antigen (PSA) levels in men participating in a prostate cancer screening program.

**Participants/Methods:** Approximately 5000 men who participated in a prostate cancer screening program were reviewed. Approximately 1400 of 5000 men were taking a statin medication. Serum PSA and total testosterone were compared between the cohort using statins and the cohort who did not indicate current statin use.

**Results:** Mean age was 61 years. Mean serum PSA level was 1.56 ng/mL in patients on statin medication and 1.48 ng/mL in patients not on a statin. This difference was not statistically significant. Serum testosterone levels were significantly lower in patients on statin medications than those not on statin medications. After adjusting for covariates such as age, body mass index, and race, statin use did show a significant association with a lower mean PSA level, but the decrease appeared to have limited clinical impact.

**Conclusions:** The authors believe that the use of statins may lower serum PSA levels, but the clinical importance appears to be limited. They believe that it is unnecessary to determine a different PSA cut-off for patients on statin medications compared to those not on statin medications.

**Reviewer's Comments:** Multiple papers dealing with the effect of statin use on prostate cancer and PSA determinations have recently been published. Many believe that data showing a decrease in incidence of prostate cancer in men on statins may be related to detection bias related to the statins causing lower PSA values. In the current study, on univariate analysis there was no statistically significant difference in PSA levels in men on statins compared to men who do not take statins. On the other hand, a multivariate analysis did show a statistically lower PSA in men who were taking statins. The magnitude of the difference, however, did not in the authors' opinion constitute a clinically important change. These authors do not believe that PSA needs to be looked at differently in patients on statins and those not on statins as far as a cut-off point to determine whether or not a prostate biopsy should be performed to rule out prostate cancer. There are several methodologic problems associated with this study. For instance, the pre-statin serum PSA levels of patients receiving statin medications are not known. Be that as it may, this paper will line up in the "statins do not have a significant effect on PSA levels" column if you are keeping score. The impact of statins on PSA levels and on the risk of prostate cancer will require much more thought and many more studies to sort out. (Reviewer-George S. Benson, MD).

**Keywords:** Statins, Serum Prostate-Specific Antigen

**Print Tag:** Refer to original journal article
In men aged ≥65 years, high serum estrone levels are associated with an increased risk of prostate cancer.

**Objective:** To determine whether serum testosterone, estradiol, estrone, and sex hormone-binding globulin are associated with the subsequent development of prostate cancer.

**Design/Participants:** A case-cohort study was conducted in men aged ≥65 years.

**Methods:** At a mean follow-up of 4.7 years, men with incident-confirmed prostate cancer were compared with a cohort of men who had not been diagnosed with prostate cancer. Serum testosterone, estradiol, estrone, and sex hormone-binding globulin were assayed at baseline and the association between incident prostate cancer and each sex hormone were evaluated.

**Results:** High serum estrone levels correlated to an increased risk of prostate cancer. The risk of prostate cancer among those men in the 3 highest quartiles for serum estrone was nearly 4-fold higher. The other sex hormones were not associated with the risk of developing prostate cancer.

**Conclusions:** The authors believe that higher estrone levels are strongly associated with an increased risk of incident prostate cancer.

**Reviewer's Comments:** Most prior studies, particularly case-controlled studies, have found no association between any sex hormone and prostate cancer. Nevertheless, the role of sex hormones in the pathogenesis of prostate cancer continues to be discussed and debated. The androgen:estrogen ratio and the influence of estrogen receptors on the prostate in the development of prostate cancer have been suggested as being important contributors to prostate cancer pathogenesis. This is the first paper of which I am aware that implicates estrone as being related to prostate cancer. The authors note that epidemiologic data show that African American men, who have the highest risk for developing prostate cancer, have significantly higher plasma estrone levels than do European Americans. Although there are some methodological problems with this study, the results are interesting and I am sure that we will see further papers dealing with the subject of estrone and the pathogenesis of prostate cancer. (Reviewer-George S. Benson, MD).

**Keywords:** Prostate Cancer, Serum Estrone Levels

**Print Tag:** Refer to original journal article