Citalopram effectively reduces hot flashes without interfering with tamoxifen metabolism via the CYP2D6 pathway.

**Background:** Since hot flashes degrade quality of life and decrease women's willingness to undergo hormonal therapy for breast cancer, better options for management are needed. Citalopram, a selective serotonin re-uptake inhibitor used for management of depression, has been shown not to interfere with tamoxifen metabolism via the CYP2D6 pathway making it an attractive drug for management of hot flashes in women taking tamoxifen.

**Objective:** To compare 3 doses of citalopram with placebo for control of hot flashes.

**Design:** Randomized, double-blind, cooperative group trial.

**Participants:** 254 women experiencing at least 14 hot flashes per week for 1 month were included. Twenty-nine percent of citalopram and 24% of placebo patients were on an aromatase inhibitor (AI), tamoxifen (T), or raloxifene (R). Patients could not be on antineoplastic or antidepressant medicines or have evidence of active cancer. A history of breast cancer was not exclusionary.

**Methods:** Hot flashes were scored individually from 1 to 4 (mild, moderate, severe, very severe) and tallied daily to produce weekly averages.

**Interventions:** Placebo (1, 2, or 3 tablets/day) or daily citalopram 10 mg, 20 mg, or 30 mg/d for 6 weeks following 1 week on no medication.

**Results:** Decreases in hot flash scores for citalopram patients over the 6-week study interval were 7.0 (49%) for 10 mg/d, 7.7 (50%) for 20 mg/d, and 10.7 (55%) for 30 mg/d compared with 2.0 (23%) for placebo patients ($P \leq 0.002$). The frequency of hot flashes also declined significantly in the respective treatment groups 3.6 (46%), 3.9 (43%), and 4.5 (50%) compared with placebo (1.4; 20%) ($P < 0.001$). Differences in scores and frequencies between citalopram treatment groups were not significant. Citalopram's effectiveness was not different for women taking AI's, T or R, and those not on these medications. Breast cancer history did not impact citalopram's effect. Citalopram was well tolerated with no significant difference in adverse effects between treated and placebo patients. Citalopram treatment resulted in significantly less hot flash-related distress and significantly more hot flash control satisfaction. Six of 10 areas assessed by the Hot Flash Related Daily Interference Scale showed statistically significant improvement with citalopram, and all 10 showed numerical superiority over placebo. Hot flash score reductions of 46% to 54% resulted in significantly improved sleep, mood, work, social activity, and enjoyment of life.

**Conclusions:** The authors conclude that citalopram significantly improves hot flashes with little or no toxicity and recommend a 20-mg/day dose to produce the most beneficial effect on daily activities.

**Reviewer's Comments:** Twenty mg of citalopram daily appears to be a safe and effective treatment for hot flashes whether or not they are related to hormonal breast cancer medications. Even though anger/hostility and tension/anxiety were significantly reduced in treated patients, the doses used appeared to be too low to address global depression. (Reviewer-Alan B. Grosbach, MD).

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Keywords: Hot Flashes, Citalopram, Postmenopausal Symptoms

Print Tag: Refer to original journal article
Based on these results, cyclophosphamide plus an anthracycline may still be preferred as first-line treatment for metastatic breast cancer with docetaxel alone or in combination with another agent as a second-line or alternative first-line option.

**Background:** The role of taxanes combined with anthracyclines in the first-line treatment of metastatic breast cancer (MBC) has not been established.

**Objective:** To compare the efficacy of epirubicin/cyclophosphamide with epirubicin/docetaxel in first-line treatment of women with MBC.

**Design:** Randomized, phase III, multicenter trial.

**Participants:** 236 women who had received no prior chemotherapy for MBC and whose cumulative adjuvant doses of either doxorubicin or epirubicin were <300 mg/m2 or <420 mg/m2 were included. Brain metastases and bone-only disease were exclusionary.

**Methods:** Tumor assessments were made at the end of every second cycle and then every 2 months.

**Interventions:** Epirubicin 90 mg/m2 plus cyclophosphamide 600 mg/m2 (EC) or epirubicin 75 mg/m2 plus docetaxel 75 mg/m2 (ED) every 3 weeks for a planned 6 cycles. Two additional cycles were allowed if maximum benefit had not been reached after the first 6. Prophylactic hematopoietic growth factor support was not permitted.

**Results:** The study was closed early due to poor accrual, with 111 patients randomized to EC and 125 to ED (planned goal, 173/arm). Overall response rates of 42.4% for EC and 47.2% for ED were not statistically different. One- and 2-year progression-free survival (PFS) rates for EC were 43.9% and 19.3%, respectively, compared with 44.6% and 19.9%, respectively, for ED (not statistically different). Median time to progression was virtually identical (10.1 vs 10.3 months). EC patients had a median overall survival of 19.9 months compared with 30.0 months for ED patients, but the difference was not statistically significant ($P=0.21$). Overall survival at 1 and 2 years was 65.8% and 43.3%, respectively, for EC patients versus 75.8% and 57.4%, respectively, for ED patients. ED was associated with a statistically significantly higher rate of leucopenia (80.8% vs 73.9%), but no other adverse event rates (including febrile neutropenia) demonstrated significant differences. One patient in each arm developed congestive heart failure.

**Conclusions:** Both EC and ED are highly effective combinations for first-line metastatic breast cancer treatment.

**Reviewer's Comments:** This study's early closure resulted in insufficient statistical power to detect a 15% superiority in response rate with ED. Nevertheless, the apparent equivalence of the 2 regimens provides flexibility in the choice of treatment for metastatic breast cancer patients. (Reviewer-Alan B. Grosbach, MD).

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**Keywords:** Anthracyclines, Chemotherapy, Docetaxel, Epirubicin, Metastases

**Print Tag:** Refer to original journal article
There are no significant differences in ipsilateral breast tumor recurrence rates after accelerated partial breast irradiation based on American Society for Radiation Oncology (ie, ASTRO) groups.

**Objective:** To determine outcomes after accelerated partial breast irradiation (APBI).

**Design:** Prospective multicenter registry.

**Methods:** The authors evaluated data from a prospective registry trial for the MammoSite device that delivers APBI with a balloon catheter. A total of 97 institutions participated and enrolled patients from 2002 through July 2004. All patients underwent breast-conserving surgery plus MammoSite APBI. The patients were categorized into 3 groups based on the American Society for Radiation Oncology (ASTRO) Consensus Statement. The 3 groups were "suitable," "cautionary," and "unsuitable" based on several patient and tumor characteristics, including age, tumor size, grade, estrogen receptor (ER) status, and margins. Ipsilateral breast tumor recurrence (IBTR) was defined as recurrence in the treated breast before or at the time of regional lymph node failure, or distant metastasis.

**Results:** The authors identified 1025 patients with sufficient information to categorize into the 3 ASTRO groups (suitable, 41%; cautionary, 42%; and unsuitable, 17%). At a median follow-up of 54 months, there were no significant differences in IBTR rates based on ASTRO groups (suitable, 2.6%; cautionary, 5.4%; and unsuitable, 5.3%). The only predictor of IBTR was ER-negative status. Likewise, there were no significant differences between the 3 groups in regional lymph node failure, disease-free survival, cause-specific survival, or overall survival; only the rate of distant metastases was associated with ASTRO grouping. A separate analysis was performed on patients with ductal carcinoma in situ; the only variables associated with IBTR were age <50 years and close-positive margins.

**Conclusions:** The authors conclude that the ASTRO groups for the use of APBI failed to differentiate between patients who may or may not benefit from MammoSite APBI.

**Reviewer's Comments:** The overall local recurrence rate after APBI was low in all 3 groups. Nevertheless, the use of APBI should be limited until the outcomes of the NSABP-B39/RTOG-0413 clinical trial are available. (Editor's Note by Jonathan J. Beitler, MD, MBA: I think that a 2.6% versus 5.4% difference may be clinically, if not statistically, significant. The study may have been underpowered.) (Reviewer-Todd M. Tuttle, MD).

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Keywords: Accelerated Partial Breast Irradiation, Guidelines, Outcomes

Print Tag: Refer to original journal article
Ixabepilone attacks the same cellular target, microtubules, as taxanes but in a different way, rendering it active against both anthracycline- and taxane-resistant tumors.

**Background:** Ixabepilone is an antimicrotubule drug of a class that binds to microtubulin differently than taxanes. It has a low susceptibility to drug resistance mechanisms and has demonstrated clinical activity in metastatic breast cancer among patients whose disease was resistant to both anthracyclines and taxanes.

**Objective:** To determine the survival impact of adding ixabepilone to capecitabine for treatment of metastatic breast cancer previously treated with both anthracyclines and taxanes.

**Design:** Randomized, multinational phase III trial.

**Participants:** 1198 women with measurable or evaluable metastatic breast cancer previously treated with both an anthracycline and a taxane as part of ≤2 chemotherapy regimens (including adjuvant).

**Interventions:** Ixabepilone 40 mg/m² (3-hour IV infusion) on day 1 of a 3-week cycle plus oral capecitabine 1000 mg/m² twice daily on days 1 through 14 (IC) of a 3-week cycle or oral capecitabine alone (1250 mg/m² twice daily on days 1 through 14 of a 3-week cycle; C).

**Methods:** Patients remained on assigned treatment until progression of disease or intolerable toxicity.

**Results:** Overall survival (OS) did not differ significantly between the 2 groups (IC median, 16.4 months; C median, 15.6). More IC than C patients had Karnofsky performance status (PS) of 70% to 80% (32% vs 25%, respectively) possibly affecting survival. For example, patients with PS of 70% to 80% had a median OS of 13 months compared with 18 months for those with a PS of 90% to 100%. After adjusting for this imbalance, IC patients’ OS was superior (HR, 0.85; P =0.0231). Also, symptomatic IC patients with a PS of 70% to 80% had an OS of 14.0 months compared with 11.3 months for comparable C patients (HR, 0.76). Sixty-five percent of IC and 71% of C patients received post-study treatment. The difference represented mostly more taxane use in C patients (24% vs 16%). IC did improve median progression-free survival (PFS; 6.24 months vs 4.4 months; HR, 0.79; P =0.0005) and overall response rate (43% vs 29%; P <0.0001). Response durations were similar (6.1 vs 6.3 months). Ixabepilone benefit was observed in poor prognosis subgroups, including women with triple-negative tumors and those relapsing within 1 year of adjuvant therapy. IC treatment was associated with more grade 3 or 4 peripheral neuropathy than C treatment (24.7% vs 1.2%), more fatigue (11.8% vs 3.2%), leukopenia (63% vs 7%), neutropenia (73% vs 9%), thrombocytopenia (6% vs 2.8%), and febrile neutropenia (7% vs 0.6%). Other toxicity rates were low, except hand-foot syndrome, which occurred in equal frequencies in both groups (21% and 20%). Peripheral neuropathy required discontinuation of one or both drugs among 26% of IC patients. This side effect was usually reversible within 4 to 6 weeks.

**Conclusions:** The addition of ixabepilone to capecitabine improves response rate and PFS compared with capecitabine alone in the treatment of metastatic breast cancer patients previously treated with anthracyclines and taxanes.

**Reviewer’s Comments:** Ixabepilone’s low susceptibility to drug resistance mechanisms holds promise for its future importance in breast cancer and perhaps other tumor management. (Reviewer-Alan B. Grosbach, MD).

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Keywords: Metastases, Ixabepilone, Capecitabine, Progression-Free Survival

Print Tag: Refer to original journal article
Cancer patients who smoke need to be advised of both the benefits of quitting as well as the immediate and long-term health risks of continuing their habit; psychological and medical support should be offered.

**Background:** Lung cancer accounts for the deaths of more Americans than breast, colorectal, and prostate cancers combined, yet Americans continue to smoke even after being diagnosed with smoking-related cancers.

**Objective:** To review issues associated with smoking among cancer patients.

**Design:** Literature review.

**Results:** Nearly 75% of hospitalized cancer patients are current (approximately 25%) or former (approximately 48%) smokers. Current smokers need to be told in a firm but supportive manner that they should quit because their quality of life will improve (less dyspnea, better energy level, and improved mood/sleep), and their treatment outcome will be positively impacted (eg, lung, renal cell, breast, cervical, prostate, and bladder cancers, Hodgkin's and non-Hodgkin's lymphomas). In addition, their risk of developing second cancers will be lower (eg, lung, head and neck, and breast cancer). Hospitalization represents a "teachable moment" for cancer patients who smoke allowing the hospital's resources to be mobilized to address the problem. Moreover, because most patients are motivated to participate in their cancer treatment, they need to know that a commitment to smoking cessation represents an important opportunity to optimize their outcome. The immediate rewards include symptomatic improvement as well as a heightened sense of personal empowerment. Both psychological and medical support is necessary to maximize the results of cessation attempts. A nonjudgmental attitude on the part of caregivers contributes to the former, while medications reduce nicotine craving and withdrawal symptoms. Because most withdrawal symptoms peak during the first 3 days of abstinence, pharmacological intervention during hospitalization may be especially valuable in promoting the long-term goal of smoking cessation.

**Conclusions:** A comprehensive program to help cancer patients stop smoking has proven benefit in improving quality of life during and after treatment. Such a program needs to include both psychological and medical components. Treatment initiated in the hospital should be followed up for at least 1 month after discharge.

**Reviewer’s Comments:** This article highlights both the benefits cancer patients derive from quitting smoking and the comprehensive nature of the support they need to have a good chance of success. Oncologists need to be proactive in helping cancer patients who are smokers to quit their habit. (Reviewer-Alan B. Grosbach, MD).

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Keywords: Tobacco Use, Withdrawal Symptoms, Care of Smokers

Print Tag: Refer to original journal article
Higher Doses of Whole Brain Radiation Improves Intracranial Control

Randomized Comparison of Whole Brain Radiotherapy, 20 Gy in Four Daily Fractions Versus 40 Gy in 20 Twice-Daily Fractions, for Brain Metastases.

Graham PH, Bucci J:

Int J Radiation Oncology Biol Phys 2010; 77 (July 1): 648-654

Higher doses of whole brain radiation for brain metastases improve intracranial control, but survival is not affected.

Background: According to our authors, patients with brain metastases have an overall survival of approximately 6 months, but there is evidence that higher radiation doses improve the outcome of patients who are selected for having a superior prognosis. One of the authors' underlying presumptions is that larger fraction sizes increase the risk of radiation-induced dementia.

Objective: To determine whether greater radiation doses delivered in a short time, but not using larger fraction sizes, would improve intracranial control and improve patients' quality of life (QOL).

Design: Prospective randomized trial from the St. George Hospital in Kogarah, Australia.

Participants: Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of <3, stable or absent extracranial disease (ie, no progression in the preceding 2 months), and a life expectancy of >2 months.

Interventions: Patients were randomized to 40 Gy in 20 twice-daily fractions or 20 Gy in 4 daily fractions.

Methods: For patients with a single brain metastasis, biopsy and excision were recommended and, thereafter, whole brain radiation. Imaging was done at 2 months and then symptomatically driven. The European Organization for Research and Treatment of Cancer Quality of Life (EORTC QOL) questionnaire was administered monthly for the first year, bimonthly the second year, and every 6 months thereafter. Salvage re-irradiation, radiosurgery, and salvage craniotomy were allowed.

Results: 113 patients were recruited; 91% completed the 40-Gy hyperfractionation series and 98% completed the 20-Gy series. Four of the 5 non-completers in the hyperfractionation arm were due to disease progression. Primary intracranial progression occurred in 44% of the hyperfractionation, high-dose group versus 64% in the 20-Gy arm ($P=0.03$). Death was attributed to central nervous system progression in 32% of hyperfractionation, high-dose group patients versus 52% of 20-Gy patients ($P=0.03$). Survival was nearly identical. Attrition meant that QOL results were not generally available after the 9- to 12-month initial follow-up. Cognitive function did not differ significantly between the 2 groups. If anything, QOL for the 20-Gy patients seemed to improve.

Conclusions: The higher dose radiation improves intracranial control but not survival.

Reviewer's Comments: It is interesting that 40 Gy in 20 twice-daily fractions had about the same cognitive results as 20-Gy in 4 fractions. My presumption is that the authors were correct, and the lower fraction size allowed better tolerance to a higher total dose than the 5 Gy per fraction in the low-dose arm. RTOG 95-08 showed that when stereotactic radiosurgery was added to whole brain radiation, there was improved functional autonomy, intracranial control, and for patients with a single brain metastases, improved survival and certainly describes an aggressive standard of care for selected patients. For better prognosis patients who cannot receive stereotactic radiosurgery, 40 Gy in 20 twice-daily fractions may be a reasonable choice. (Reviewer- Jonathan J. Beitler, MD, MBA).

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Keywords: Brain Metastases, Whole Brain Radiotherapy, Quality of Life

Print Tag: Refer to original journal article
Objective: To determine the clinical utility of routine chest CT among patients with colorectal carcinoma.

Design: Retrospective single-institutional study.

Methods: The authors reviewed the impact of staging chest CT for patients with newly diagnosed colorectal cancer. Chest CT was routinely performed for patients with colorectal cancer. When staging CT could not be performed before surgery because of acute presentation (obstruction, bleeding), the CT scan was done within 1 month after surgery. Lesions on chest CT were characterized as benign, malignant, or indeterminate. Indeterminate pulmonary lesions were reevaluated during follow-up. The definitive diagnosis of pulmonary metastases was based on imaging or histologic confirmation. Lesions were considered benign when they did not grow, and no increase in carcinoembryonic antigen (CEA) was observed after at least 1 year.

Results: The authors identified 200 patients who were diagnosed between 2007 and 2008. Synchronous liver, lung, and/or peritoneal metastases were identified in 60 patients (30%). Lung metastases were diagnosed on the initial CT in 6 patients (3%); 1 of these 6 patients actually had a benign lesion. Indeterminate lung lesions were found on 50 patients (25%); among these patients, 8 had lung metastases, 2 had primary lung cancer, and 15 had no diagnosis. Overall, 13 of the 200 patients (7%) had synchronous lung metastases. In 6 patients, the metastases were confined to the lung. Synchronous lung metastases were more common among rectal cancer patients (10%) as compared with colon cancer patients (5%).

Conclusions: The authors conclude that chest CT is not recommended for routine staging colorectal cancer. They also conclude that chest CT has several disadvantages, such as costs, radiation exposure, and uncertainly of the frequent finding of indeterminate lesions.

Reviewer's Comments: The incidence of synchronous lung metastases was low in this study. Presumably, chest radiography would detect some synchronous lung metastases. So, the absolute benefit of routine chest CT is probably quite low. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Colorectal Carcinoma, Diagnostics, Chest CT

Print Tag: Refer to original journal article
The presence of positive HPV in the tumor of patients with oropharyngeal cancer predicts a 58% reduction in the risk of death after adjustment for favorable prognostic factors.

**Background:** The Radiation Therapy Oncology Group (RTOG) was working on a fractionation study when the human papillomavirus type 16 (HPV-16) oropharyngeal epidemic hit the United States. Believing that both accelerated radiation and concurrent chemotherapy improved survival, RTOG 0129 was designed to study the question of whether accelerated fraction radiation was superior to standard radiation when each group was given chemotherapy.

**Objective:** To report the findings of RTOG 0129 with an emphasis on the effect of HPV status on survival in the patients with oropharyngeal cancer. The primary end point of RTOG 0129 was survival.

**Design:** RTOG 0129 was a multicenter randomized trial. Analysis of the effects of HPV16 was performed by a retrospective review of data from the randomized trial.

**Participants:** 721 patients with Stage III or IV squamous cell cancers of the oral cavity, oropharynx, larynx, or hypopharynx without distant metastases were analyzed. Study accrued from 2002 to 2005, and 60% of patients had oropharyngeal cancers.

**Interventions:** Patients were randomized to concurrent high-dose cisplatin with either standard-fractionation radiation or concomitant boost radiation. Standard radiation was 70 Gy in 35 fractions over a period of 7 weeks. Concomitant boost was 72 Gy in 42 fractions over 6 weeks. This was achieved with twice daily treatment for the last 12 treatment days.

**Methods:** HPV analysis was performed only for patients with oropharyngeal primaries.

**Results:** There were no early or late toxicity differences between the 2 arms. With a median follow-up of 4.8 years, there was no significant difference in the 3-year rate of overall survival (70.3% for the accelerated group versus 64.3% for the standard-fractionation group; \( P =0.18 \)). There were no significant differences in progression-free survival (PFS) or patterns of failure between the 2 groups. The study had an 80% statistical power to detect a 25% relative reduction in the risk of death. HPV and p16 status were determined in 75% of the oropharyngeal cancer patients. Positive HPV status was more common in never-smokers and was associated with smaller tumors, younger age, white race, better performance status, and the absence of anemia. The positive HPV group had an 82.4% 3-year survival rate compared with 57.1% in the negative HPV oropharyngeal cancer group (\( P <0.001 \)). Multivariate analysis found that age, race, performance status, tumor stage, nodal stage, and the number of pack-years of smoking were all significant determinants of overall survival. These factors were estimated to account for 9% of the difference in outcome between positive and negative HPV patients. After adjustment, positive HPV still caused a 57% reduction in death as compared to negative HPV. Positive HPV and p16 had very good agreement. The risk of death increased by 1% for each additional pack-year of smoking, and this effect was similar for positive and negative HPV patients. Positive HPV patients had better local-regional, but not distant, control.

**Reviewer's Comments:** Dr. Gillison did a great job ferreting out the HPV story. Hard to believe that the RTOG powered the study and only detect a 25% difference in survival. (Reviewer-Jonathan J. Beitler, MD, MBA).

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Keywords: Human Papillomavirus, Oropharyngeal Cancer, Fractionation, Survival

Print Tag: Refer to original journal article
Treatment with chemotherapy alone failed to control regional disease in laryngeal cancer patients having a complete histologic response at the primary site.

**Background:** Although chemoradiation has been unsuccessful in improving survival compared to primary surgery, induction chemotherapy has been predictive of favorable responses to chemoradiation. If definitive chemotherapy was curative, then acute and late effects of radiation, including significant fibrosis resulting in speech and swallowing defects, could be avoided.

**Objective:** To decide if patients with advanced laryngeal cancer who had a complete response at the primary site to chemotherapy could be managed with a chemotherapy-alone approach.

**Design:** Single institution, Phase II study from the University of Michigan.

**Participants:** Patients with confirmed and previously untreated stage III and IVA squamous cell cancers of the larynx and hypopharynx were included.

**Interventions:** All eligible patients with good renal and hearing function received 100 mg/m2 of cisplatin with 1 g/day of 5-fluorouracil (5FU) for 5 days. Patients with hearing loss or a creatinine clearance of <60 cc/minute received carboplatin (AUC=6) on day 1.

**Methods:** Tumors were assessed by direct laryngoscopy under anesthesia pretreatment and 3 weeks after induction chemotherapy. Patients with complete clinical and histologic responses at the primary site were treated with 3 additional cycles of alternating chemotherapy. Cycles 2 and 4 were identical to the induction chemotherapy. Cycle 3 was 3 treatments of weekly docetaxel (35 mg/m2) followed by 1 week of rest. Patients with a sustained complete response 8 weeks after the initial 4 cycles of chemotherapy received ANOTHER 4 cycles of alternating docetaxel and cisplatin (carboplatin) and 5FU chemotherapy.

**Results:** 32 eligible patients were enrolled in this trial and received induction chemotherapy. Four patients had complete histologic and clinical response and received chemotherapy alone. Twenty-four patients had a partial response and underwent concurrent chemoradiation, while there were 4 patients with a <50% response who received surgery with XRT. None of the 4 complete responders to induction chemotherapy were disease free at the completion of chemotherapy. All failed in the neck (3 with persistent disease and 1 with both local and regional progression). Of these 4 patients, 2 were hypopharyngeal primaries (there were 4 hypopharyngeal cancers in 32 patients), and 2 had supraglottic cancers. All 4 of the complete responders failed chemotherapy alone and received postoperative intensity-modulated radiation therapy as part of their salvage. For the 4 patients with complete response after induction chemotherapy, only 1 was alive at 3 years. One died from a carotid blowout, 1 died of distant metastases, and 1 died from regional recurrence. Among the partial-response patients, locoregional failure occurred in 6 of the 24.

**Conclusions:** Treatment with chemotherapy alone failed to control regional disease in patients having a complete histologic response at the primary site. Biology in the neck may differ from biology of the primary laryngeal cancer.

**Reviewer's Comments:** This is an outstanding paper and wonderful discussion therein. Note that only 1 of the 4 patients failed locally, and that patient could have failed from direct extension of nodal disease into the laryngeal cartilage. (Reviewer-Jonathan J. Beitler, MD, MBA).

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Keywords: Advanced Laryngeal Cancer, Organ Preservation, Chemotherapy

Print Tag: Refer to original journal article
SUV Values After Chemoradiation Categorizes Patients Into Prognostic Groups

Critical Role of Surgery in Patients With Gastroesophageal Carcinoma With a Poor Prognosis After Chemoradiation as Defined by Positron Emission Tomography.
Patnana SV, Murthy SB, et al:
Cancer 2010; July 13 (): epub ahead of print

Surgery is an independent predictor of overall survival for patients with gastroesophageal carcinoma after chemoradiation, irrespective of high or low standardized uptake value.

Objective: To determine the impact of standardized uptake value (SUV) of positron emission tomography (PET) imaging after chemoradiation for gastroesophageal carcinoma.
Design: Retrospective single-institutional study.
Participants/Methods: The authors retrospectively evaluated patients with localized gastroesophageal carcinoma treated at their center from 2002 through 2008. Pretreatment evaluations included upper gastroesophageal endoscopy, endoscopic ultrasound, and PET. The primary objective of this study was to determine the outcomes of patients based on the SUVs after chemoradiation. Patients were categorized as either high SUV or low SUV determined by the median value (4.6) in this study. All patients received a fluoropyrimidine and taxane or platinum compound concurrently with radiation. PET imaging was repeated approximately 5 to 6 weeks after completion of chemoradiation.
Results: The authors identified 204 eligible patients; most patients had adenocarcinoma. The median overall survival rate was 2.85 years for the entire cohort. The median survival rate for patients who had high SUV and did not undergo surgery was 1.22 years; the median survival rate for patients who had high SUV and did undergo surgery was 2.70 years. Among patients who had low SUV and underwent surgery, the median survival rate was 4.24 years. On multivariate analysis, surgery was an independent predictor of overall survival, irrespective of high or low SUV. Among surgical patients, low SUV status was associated with improved outcomes.
Conclusions: SUV values after chemoradiation can be used to categorize patients into prognostic groups.
Reviewer's Comments: Although high SUV after chemoradiation was associated with a worse prognosis, surgical resection was associated with an improved overall survival rate. This finding suggests that high SUV is a prognostic factor, not an exclusion factor, for surgical resection. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Gastroesophageal Cancer, Surgery, Chemoradiation, PET, Prognosis

Print Tag: Refer to original journal article
A single hepatic artery injection of 90Y-resin microsphere added to standard protracted 5-FU infusion extends time to local and overall disease progression for patients with liver metastases from colorectal cancer.

**Background:** Radioembolization with microspheres loaded with the radionuclide yttrium-90 (90Y) allows multiple hepatic metastases to be targeted with a single procedure. 90Y becomes lodged in the tumor vasculature, and over "approximately 14 days," delivers curative β-radiation while keeping the remainder of the liver parenchyma to within normal limits. (Note: half-life, 62 hours.) In a phase III study, patients with liver metastases from colorectal cancer were randomized to hepatic arterial infusion of floxuridine with/without a single injection of 90Y-resin microspheres. Patients receiving radioembolization had double the response rate and less than half the hepatic progression of chemotherapy-only patients.

**Objective:** To test the safety and efficacy of 90Y-resin microspheres in liver-limited metastatic colorectal cancer in patients in whom all other evidence-based salvage techniques had failed.

**Design:** Phase III, open-label, randomized trial from 3 institutions in Belgium.

**Participants:** Patients with metastatic colorectal adenocarcinoma not amenable to curative surgery or radioablation and resistant/intolerant of standard chemotherapy were eligible. Patients with pre-existing hepatic disease, ascites, or extrahepatic disease were ineligible.

**Interventions:** Patients were randomized as follows: arm A, protracted IV infusion of 5-FU (300 mg/m2) on days 1 to 14 every 3 weeks until progression; or arm B, radioembolization plus the same schedule of 5-FU. For ethical reasons, patients in arm A were allowed to cross-over to receive radioembolization after progression.

**Methods:** The procedure for radioembolization was standardized. Liver angiography was performed, and potential dangerous side branches and anastomoses were occluded with coil embolization. Lung shunting was evaluated by injecting technetium-labeled macroaggregated albumin into the hepatic artery. Lung shunting had to be <20%. All patients were treated once and observed overnight. The dose of 90Y was calculated using body surface area and extent of tumor and was modified for hepatopulmonary shunting.

**Results:** 23 patients were randomized to each arm. One arm B patient was ineligible because of bone metastases, and 1 arm B patient could not be treated because of technical issues. Using RECIST criteria, the overall response rates were 0 of 23 patients (0%) for arm A and 2 of 21 patients (9.5%) for arm B. Disease control rates (partial response and stable disease) were 35% for arm A and 86% for arm B. Median time to liver progression was 2.1 and 5.5 months, respectively. Grade 3 or 4 toxicities were seen in 6 patients after 5-FU monotherapy and in 1 patient after radioembolization.

**Conclusions:** This randomized trial met its primary end point by demonstrating that a single hepatic artery injection of 90Y-resin microsphere added to standard protracted 5-FU infusion extended the time to local and overall disease progression.

**Reviewer's Comments:** The authors conclude that RECIST criteria lacked sensitivity due to necrosis, hemorrhage, and cystic changes, making volume measurement unreliable. This is a great deal of effort for a relatively small gain. There are few data to suggest increasing resectability. (Reviewer-Jonathan J. Beitler, MD, MBA.)

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Keywords: Liver Metastases, Radioembolization

Print Tag: Refer to original journal article
Objective: To evaluate the outcomes of a new procedure for performing bedside peritoneal lavage for gastric cancer.

Design: Prospective single-institutional study.

Participants: The authors enrolled 113 patients with gastric adenocarcinoma. Inclusion criteria included T3 or deeper tumors, absence of distant metastases, no previous therapy, no previous laparotomy, and no active bleeding or obstruction.

Methods: Preoperative peritoneal lavage and tube insertion were performed with local anesthesia at the bedside. The tube was placed into the peritoneal cavity, and saline 500 cc was infused intraperitoneally. Cytology was performed on the returned lavage fluid. If the cytology was positive, then gastrectomy was not performed. If the cytology was negative, then laparotomy was performed along with a second lavage.

Results: The mean procedure time was 25 minutes. Thirty-five patients (31%) were diagnosed with positive cytology preoperatively; 78 patients (69%) were cytology negative. Peritoneal cytology did not correlate with age, gender, tumor location T stage, or N stage but did correlate with histologic type. All patients who had negative preoperative peritoneal cytology underwent laparotomy; 9 patients (11.5%) had peritoneal dissemination. Thus, the false-negative rate for the bedside peritoneal lavage was 20.5%. The mean survival rate for all patients was 24 months. For patients with positive cytology, the mean survival rate was 18 months, and the 2-year survival rate was 27%. For patients with negative cytology, the mean survival rate was 31 months, and the 2-year survival rate was 83%.

Conclusions: Bedside peritoneal lavage with cytology is a safe and efficient method to determine peritoneal dissemination for patients with T3 gastric cancer.

Reviewer’s Comments: Although positive peritoneal cytology is associated with worse prognosis for patients with gastric cancer, it is not universally accepted as an exclusion criterion for resection without visible metastases. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Gastric Cancer, Peritoneal Lavage

Print Tag: Refer to original journal article
Pegylated liposomal doxorubicin produces much less lingering toxicity (such as sensory neuropathy and alopecia) compared with paclitaxel when combined with carboplatin for the treatment of relapsed ovarian cancer.

**Background:** New treatments are needed for the majority of patients with advanced ovarian cancer who typically relapse despite complete response to initial therapy. Pegylated liposomal doxorubicin (PLD) is an effective salvage agent whose role in second-line combination therapy is undefined.

**Objective:** To compare the efficacy and safety of carboplatin/PLD (CD) with carboplatin/paclitaxel (CP) in patients with relapsed platinum-sensitive ovarian cancer.

**Design:** Randomized phase III multi-national trial.

**Participants:** 973 patients with cancers of the ovary or fallopian tube or extra-ovarian papillary serous tumor who relapsed ≥6 months after first- or second-line platinum-based chemotherapy.

**Methods:** Tumor assessments were performed every 3 months during treatment and for the first 2 years, then every 6 months for 5 years. Echocardiography or MUGA scans were performed to determine left ventricular ejection fraction (LVEF) at baseline and before each chemotherapy cycle if the cumulative doxorubicin dose was >450 mg/m².

**Interventions:** 6 cycles of either carboplatin (AUC 5) plus PLD 30 mg/m² every 4 weeks or carboplatin (AUC 5) plus paclitaxel 175 mg/m² every 3 weeks. Patients with stable disease or partial response after 6 cycles of treatment remained on treatment until progression or toxicity.

**Results:** With a median follow-up of 22 months, the median progression-free survival (PFS) was 11.3 months for CD and 9.4 months for CP (HR, 0.823; \( P = 0.005 \)). The treatment arm was the only factor significantly associated with PFS on multivariate analysis. Grade 3 to 4 neutropenia was more frequent with CP (45.7% vs 35.2%); grade 3 to 4 thrombocytopenia was more frequent with CD (15.9% vs 6.2%). Of CD patients, 12% experienced palmar plantar dysesthesia (primarily grade 2) compared with 2.2% of patients with CP. CP was associated with more grade 2 or higher sensory neuropathy (26.9% vs 4.9%) and more grade 2 or higher allergic/hypersensitivity reactions (18.8% vs 5.6%). CD caused significantly more nausea (35.2% vs 24.2%), vomiting (22.5% vs 15.6%), and mucositis (13.9% vs 7%); CP caused more arthralgia/myalgia (19.2% vs 4.0%). Fatigue rates were equivalent between groups. Of CP patients, 83.6% had grade 2 or higher alopecia versus 7% of CD patients.

**Conclusions:** Carboplatin/pegylated liposomal doxorubicin is a more effective, less toxic treatment option than carboplatin/paclitaxel for women with platinum-sensitive relapsed ovarian cancer.

**Reviewer’s Comments:** For unknown reasons, pegylated liposomal doxorubicin was associated with far fewer hypersensitivity reactions to carboplatin. In a trial that compared CD with single-agent carboplatin, the incidence of such reactions was 23% for carboplatin compared with 0% for the combination. (Reviewer-Alan B. Grosbach, MD).

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Keywords: Pegylated Liposomal Doxorubicin, Paclitaxel, Relapsed Ovarian Cancer

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How to Determine Optimal Peripheral Margins for DFSP

*Dermatofibrosarcoma Protuberans: How Wide Should We Resect?*

Farma JM, Ammori JB, et al:

*Ann Surg Oncol* 2010; 17 (August): 2112-2118

The local recurrence rate for patients with dermatofibrosarcoma protuberans and final negative margins is very low.

**Objective:** To determine the optimal peripheral margin for patients with dermatofibrosarcoma protuberans (DFSP).

**Design:** Retrospective analysis of the experience from 2 institutions.

**Participants:** The authors conducted a retrospective review of the records of patients with DFSP treated between 1991 and 2008 at 2 separate institutions. Patients with DFSP with sarcomatous transformation were excluded. The authors evaluated clinicopathologic factors, excision margin width, number of excisions, use of postoperative radiation, and local recurrence rates. A negative margin was defined as no evidence of DFSP at the inked tangential margin.

**Results:** The authors identified 204 patients with DFSP; 63% were female. The median patient age was 41 years. The most common primary site was the trunk (65%), followed by the head/neck (14%), lower extremity (12%), and upper extremity (9%). The median margin width was 2 cm. Only 1 resection was needed to achieve negative margins in 81% of patients, and 16% required 2 excisions; only 3% of patients required ≥3 excisions. Primary closure was performed for 69% of all resections. Nine patients (4%) received adjuvant radiation; 6 received radiation for persistently positive margins. At a median follow-up of 64 months, 2 patients (0.9%) experienced local recurrence; both patients had positive margins and had head/neck DFSP.

**Conclusions:** The local recurrence rate is very low for patients with DFSP who undergo resection and wide excision with relatively narrow margins (median, 2 cm). As a result, most patients can receive primary closure after excision.

**Reviewer’s Comments:** DFSP is a rare tumor with a predilection for local recurrence. This study demonstrated a very low recurrence rate for patients with final negative margins; postoperative radiation therapy can be safely avoided in the majority of patients. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Sarcoma, Dermatofibrosarcoma Protuberans, Margins

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Urine Cytology Not Always Needed in Asymptomatic Microscopic Hematuria

Utility of Urine Cytology in the Workup of Asymptomatic Microscopic Hematuria in Low-Risk Patients.

Feifer AH, Steinberg J, et al:

Urology 2010; 75 (June): 1278-1284

Voided urinary cytology adds little to the evaluation of low-risk patients who present with asymptomatic microscopic hematuria.

Background: Both the American Urologic Association Best Practice Policy and the Canadian Urologic Association guidelines recommend urine cytology as part of the diagnostic evaluation of low-risk patients who present with asymptomatic microscopic hematuria.

Objective: To determine the value of voided urine cytology in this group of patients.

Methods: The records of 200 consecutive low-risk patients who presented with asymptomatic microscopic hematuria were retrospectively reviewed. All of these patients underwent upper urinary tract imaging studies, cystoscopy, and a voided urine cytology.

Results: None of the 200 patients had a positive urinary cytology. Approximately 10% had atypical cytology, and approximately 90% had negative urinary cytology. Eight of the 200 patients (4%) had a low-grade transitional cell carcinoma of the bladder diagnosed by cystoscopy. In these 8 patients, the cytology was negative in 4 patients and atypical in 4 patients. No upper urinary tract or renal cancers were identified. The cost of performing urinary cytology was approximately $250 per patient.

Conclusions: The authors believe that, in the evaluation of low-risk patients with asymptomatic microscopic hematuria, urine cytology does not provide any diagnostic benefit and adds cost to the evaluation.

Reviewer’s Comments: This study again emphasizes the fact that patients, particularly older patients, who present with asymptomatic microscopic hematuria need to be evaluated. Eight of the 200 patients in this study were found to have a transitional cell carcinoma of the bladder. Most urologists, including the authors of this paper, advocate the use of urine cytology in symptomatic patients or in patients who have risk factors for bladder cancer, including smoking. Patients with asymptomatic microscopic hematuria who are at low risk are often seen in the urologist’s office. The question is, in addition to upper tract imaging and cystoscopy, whether these patients also need to have a voided urine cytology performed. The results of this relatively small study argue strongly that, in these low-risk patients, voided urinary cytology adds nothing to the diagnostic evaluation. Based on data, I would agree with the authors that the performance of urine cytology in low-risk patients with asymptomatic microscopic hematuria can probably be discarded. (Reviewer-George S. Benson, MD).

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Keywords: Urine Cytology, Asymptomatic Microscopic Hematuria

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Quality Colonoscopy Redefined

Quality Indicators for Colonoscopy and the Risk of Interval Cancer.
Kaminski MF, Regula J, et al:


Cecal intubation does not correlate with the risk of subsequent colon cancer.

Background: Quality indicators for colonoscopy are defined by numerous professional and governmental entities. Two commonly used indicators are adenoma detection rate and cecal intubation. How valid either of these quality indicators is remains in question.

Objective: To determine the validity of adenoma detection rate and cecal intubation as quality indicators for colorectal cancer screening colonoscopy.

Design: Retrospective review of prospectively collected data.

Participants: 45,026 patients and 186 endoscopists followed in a screening program.

Methods: All endoscopists had to contribute ≥30 cases in the patient sample. Colonoscopy data were retrieved from the screening program's database. Patients with interval colon cancer were identified by a patient identifier linked to cancer databases. In patients, 42 interval colon cancers were found. Adenoma detection rate was defined as total patients screened with ≥1 adenoma. When adenomas were detected in a screening colonoscopy, all needed to be removed to include the patient. Cecal intubation was defined as a description of the cecum in the screening report. Primary outcome was to correlate quality indicators with risk for subsequent colon cancer. A multivariate Cox proportional hazard analysis was used.

Results: Rate of cecal intubation varied from 83% to 98% for the various endoscopists. Adenoma detection rate ranged from 10% to >20%. Interval cancer was related to adenoma detection rate with odds ratio from 11 to 13 depending upon rate of adenomas detected. No relationship was found between cecal intubation and interval colon cancer.

Conclusions: Adenoma detection rate was a better quality indicator when interval colon cancer was the primary concern while cecal detection rate was not correlated.

Reviewer's Comments: This study challenges a quality indicator for colonoscopy. They suggest that cecal intubation does not correlate with lower risk of interval colon cancer, but that the adenoma detection rate does. The authors did not measure withdrawal time which is another quality indicator which may or may not be helpful. Data appear clear, but is the correlation with colonoscopy or disease? More adenomas suggest a patient at risk for colon cancer. Patients with cancer at the initial screening colonoscopy were excluded from the study population. However, the patient with multiple polyps, even after removing all of them as demanded by protocol, would be at the greatest risk for subsequent colon cancer. Alternatively, since the cecal intubation rate was so high in this study, maybe we really do not have enough data to exclude cecal intubation as a surrogate for quality. I doubt if this paper will make cecal intubation disappear as a quality indicator for screening colonoscopy. (Reviewer-John A. Weigelt, MD).

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Keywords: Colon Cancer Diagnosis, Adenoma Detection Rate, Cecal Intubation

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Second Opinion Pathology Review Recommended for Prostate Needle Biopsies

The Value of Mandatory Second Opinion Pathology Review of Prostate Needle Biopsy Interpretation Before Radical Prostatectomy.
Brimo F, Schultz L, Epstein JI:
J Urol 2010; 184 (July): 126-130

In a second opinion pathology review of prostate needle biopsies before radical prostatectomy, prostate cancer could not be confirmed in 1.2% of cases.

Objective: To determine the value of second opinion pathology review of prostate needle biopsies before radical prostatectomy.

Methods: 855 cases originally diagnosed as prostate adenocarcinoma were reviewed at the time of referral for radical prostatectomy. The original pathology reports from the referring institution were compared with the reviewed pathology reports.

Results: Of the 855 cases initially diagnosed as prostate cancer from an outside institution, prostate cancer was confirmed in 844 cases (98.8%). Of the 11 cases with a disparate diagnosis of cancer or no cancer, upon review, 9 were thought to be "atypical" and 2 were benign. Major discrepancies in Gleason score were also found. A major discrepancy in Gleason score was present in 124 of the 855 cases; 46% were upgraded, and 54% were downgraded with regard to Gleason score.

Conclusions: The authors believe the unconfirmed cancer rate is 1.2%. They also believe that mandatory second pathology review of prostate needle biopsies before radical prostatectomy should become routine practice.

Reviewer's Comments: The authors note that the Association of Directors of Anatomical and Surgical Pathology recommended second opinion pathology review in 1993. However, many hospitals currently do not require a second pathology review before surgery. Prior studies have shown significant diagnostic discordances that have a direct impact on treatment when pathology material is reviewed. This diagnostic disagreement is higher for certain tissues, including ovary, endometrium, soft tissue, lymphoma, cervical cytology, testis, and prostate. In this series, >1% of pathology reviewed did not find a cancer when a cancer was thought to be present. In addition, 21 of 61 patients (34%) with a final Gleason score of 8 to 10 were originally diagnosed as having a score of ≤7. Because significant discrepancies exist, the results presented in this paper indicate that a second pathologic opinion of prostate needle biopsy findings is a good idea. If I were diagnosed with prostate cancer on needle biopsy, I would certainly have the slides reviewed before undergoing radical prostatectomy. (Reviewer-George S. Benson, MD).

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Keywords: Prostate Cancer, Needle Biopsy, Second Opinion, Pathology

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In patients with non–muscle-invasive bladder cancer, surveillance cystoscopy needs to be continued after 5 years even if there has been no recurrence of the tumor.

**Objective:** To determine the recurrence and progression rates in patients with non–muscle-invasive bladder cancers who do not experience a recurrence in the 5 years after initial diagnosis.

**Methods/Participants:** During a 17-year period, 814 patients were diagnosed with non–muscle-invasive bladder cancer; 262 of these 814 patients had no tumor recurrence during the first 5 years of follow-up.

**Results:** The patients who had no recurrence for 5 years continued to be followed, and 39 (15%) showed tumor recurrence. Five patients (2%) experienced bladder cancer stage progression.

**Conclusions:** The authors believe that, even after a 5-year tumor-free period after the initial diagnosis, patients with bladder cancer need to continue to be followed. This appears to be true even in low-risk patients.

**Reviewer’s Comments:** The question of how long to follow patients with bladder cancer who do not experience a recurrence continues to be unanswered. Currently, no guideline outlines a specific schedule for low-risk patients after a 5-year tumor-free period. Because of the results presented in this paper, the authors believe that even low-risk patients (solitary Ta Grade 1 to 2 tumor) need follow-up evaluation at least once a year after a 5-year tumor-free period because the probability of recurrence is equal to that of the intermediate- and high-risk groups. They recommend that low-risk patients be followed up for at least 10 years. It is clear that patients with bladder cancer who have not experienced a recurrence for 5 years after the initial diagnosis still need to be periodically evaluated. The frequency of this evaluation and the length of time before stopping this evaluation are still unanswered questions. Patients who have not had a recurrence during the first 5 years after a bladder tumor resection are hesitant to continue with periodic surveillance cystoscopies. The data presented in this paper argue that continued surveillance cystoscopy is a good idea. If you can’t stop at 5 years, when can you stop? I do not think this question can be answered with current data. (Reviewer-George S. Benson, MD).

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Keywords: Bladder Cancer, Surveillance Cystoscopy

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