Background: The American Society of Clinical Oncology (ASCO) periodically issues technology assessments to guide physicians in managing breast cancer patients.

Objective: To update ASCO guidelines based on advancements in technology reported since 2004.

Design: Literature review and consensus development by expert panel. Design: This update was framed as the answers to 7 clinical questions.

Question 1a: What adjuvant endocrine treatments should be offered to postmenopausal hormone receptor-positive women? An aromatase inhibitor (AI) should be offered to most women initially or after 2 to 3 years of tamoxifen therapy. The absolute reduction in relapse risk from AI therapy compared with tamoxifen alone is <5%.

Question 1b: What is the appropriate duration of adjuvant therapy? AI treatment should not exceed 5 years, whether alone or after tamoxifen. Tamoxifen to round out a 5-year course is recommended for women initially on AIs who stop before 5 years. Question 1c: How long should first-line tamoxifen be used before switching to an AI? Switching from tamoxifen to an AI at 2 to 3 years is the panel's recommendation, although switching after 5 years is supported by published trial results.

Question 2: Are there populations with differing degrees of benefit from AIs versus tamoxifen? No special populations have been identified that are more likely to benefit from AIs. Male breast cancer patients should be treated with tamoxifen. Concurrent use of tamoxifen and drugs that inhibit the CYP2D6 isoenzyme (bupropion, paroxetine, and fluoxetine) should be avoided.

Question 3: What are the toxicities and risks of adjuvant endocrine therapy? Side effect profiles, comorbidities, and patient preferences should all be considered in the choice of a hormonal agent. Switching agents (AI to tamoxifen, vice versa, or AI to a different AI) is appropriate if side effects necessitate the change.

Question 4: Are AIs effective for premenopausal women? Premenopausal and perimenopausal women (at time of breast cancer diagnosis) should receive tamoxifen for 5 years. Residual ovarian function is a contraindication to AI therapy. Amenorrhea for 1 year constitutes clinical menopause, but chemotherapy, tamoxifen treatment, surgery, and comorbidities may invalidate this definition in breast cancer patients. Question 5: Can third generation AIs be used interchangeably? AI treatment results suggest a “class effect” without apparent differences in effectiveness or side effects between available agents. The panel emphasized the importance of detailed physician discussion with patients regarding the benefits and risks of hormone therapy to optimize compliance. Unexpected side effects, musculoskeletal adverse effects of AIs, and financial constraints contribute to the 30% to 40% rate of treatment discontinuation by patients.

Conclusions: Adjuvant AIs improve disease-free survival compared with tamoxifen alone.

Reviewer's Comments: These guidelines provide an excellent framework for adjuvant hormonal therapy decision making for most breast cancer patients. The authors emphasize the importance of individualization of treatment. (Reviewer-Alan B. Grosbach, MD, FACP).
Preoperative breast MRI did not accurately predict the extent of disease in patients with extensive ductal carcinoma in situ.

**Objective:** To assess the value of preoperative breast MRI for patients with ductal carcinoma in situ (DCIS).  
**Design:** Retrospective single-institutional study.  
**Participants:** 98 consecutive patients with a diagnosis of DCIS in 2007 from a community-based health care system. Of these patients, 63 underwent preoperative breast MRI after image-guided needle biopsy. One patient had bilateral DCIS, for a total of 64 cases.  
**Methods:** All patients underwent mammography and image-guided biopsy. MRI examinations were performed with a 1.5-T magnet. Residual enhancement was considered positive for residual disease. The size of DCIS on MRI used to determine overestimation or underestimation was the single largest diameter of enhancement on MRI.  
**Results:** The median patient age was 60.5 years. Breast-conserving surgery was performed in 77 cases, and mastectomy was performed in 22. The use of breast MRI was not associated with increased mastectomy rates. However, in the MRI group, 4 patients elected mastectomy based on the extent of disease on MRI. In all 4 patients, MRI overestimated the extent of disease by an average of 3.0 cm. Among patients undergoing breast-conserving surgery, the rate of positive margins was lower in the MRI group compared to the non-MRI group (21.2% versus 30.8%, respectively), but the difference did not reach statistical significance (P=0.41). MRI overestimated the size of residual disease by a mean of 2.0 cm. For patients with tumor size >2 cm, the mean overestimation was 3.2 cm. The mean underestimation size was 0.43 cm. Of the 64 cases of DCIS, the pathology and MRI results were discordant in 33% of cases: 48% had positive MRI results but no residual DCIS, while 52% had negative MRI results but had residual DCIS on pathology.  
**Conclusions:** Mastectomy should not be based on MRI results alone without biopsy confirmation of extensive or multicentric disease.  
**Reviewer’s Comments:** With the widespread adoption of breast MRI, the authors’ caution is warranted. The study did not report on the use of MRI to identify occult contralateral breast cancer among patients with DCIS. (Reviewer-Todd M. Tuttle, MD).
Range of motion and arm volumes are improved with sentinel lymph node biopsy as compared with axillary lymph node dissection in patients with stage I and II breast cancer.

**Objective:** To determine the morbidity of sentinel lymph node (SLN) biopsy and axillary lymph node dissection (ALND) for breast cancer patients.

**Design:** Prospective single-center study.

**Participants:** Patients with stage I and II breast cancer.

**Methods:** Patients with preexisting shoulder complaints were excluded. On the day before surgery, measurements, including range of motion (ROM), strength, and arm volume, were obtained from a physician or physiotherapist. The same measurements were repeated at 6 weeks, 6 months, 12 months, and 24 months. SLN biopsy was performed in a standardized fashion. If SLN metastases were identified, completion ALND was performed. Breast radiotherapy was administered to all patients who underwent breast-conserving surgery. After surgery, women received standardized instructions on exercises of the upper extremity. The authors evaluated outcomes for 3 treatment groups: SLN alone, SLN plus ALND, and ALND alone.

**Results:** The final cohort consisted of 171 patients. There were no differences in ages or body mass index among the different treatment groups. The baseline measurements were similar between the 3 groups. ROM measurements were significantly improved for the SLN-alone group as compared to either SLN-plus-ALND or ALND-alone groups. No significant differences in arm or grip strength were observed between the 3 groups. Increases in arm volume were significantly less in the SLN-alone group as compared with the ALND-alone group, but arm volume did not differ significantly between the SLN-alone and SLN-plus-ALND groups. Increases in arm volume were significantly greater among patients treated with chemotherapy. Radiation therapy was associated with significantly worse ROM. The number of lymph nodes retrieved was significantly associated with decreased ROM and increased arm volume.

**Conclusions:** ROM and arm volumes are improved with SLN biopsy as compared with ALND.

**Reviewer's Comments:** Another important finding from this study is that lymphedema continued to progress 2 years after ALND, but lymphedema did not occur in the SLN-alone group. (Reviewer-Todd M. Tuttle, MD).

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**Keywords:** Lymph Node Dissection, Arm Morbidity

**Print Tag:** Refer to original journal article
For patients with a diagnosis of breast cancer and BRCA1 or BRCA2 mutations, bilateral mastectomy effectively reduced the risk of breast cancer development, and salpingo-oophorectomy improved survival.

**Background:** Women with BRCA1 or BRCA2 mutations have greatly increased risks of developing breast and ovarian cancers. The lifetime risk of breast cancer development ranges from 56% to 84%, while the risk of developing ovarian cancer ranges from 36% to 63% for BRCA1 carriers and from 10% to 27% for BRCA2 carriers. Salpingo-oophorectomy (SO) decreases the risk of both ovarian and breast cancer development.

**Objective:** To determine the effect of risk-reducing mastectomy and risk-reducing SO in women with BRCA1 and BRCA2 mutations.

**Methods:** Women at risk, whether or not they had a history of breast cancer, were identified at 22 centers. Women who declined either mastectomy or SO were offered intense screening as per center guidelines. Women who developed cancers within the first 6 months were excluded (considered a preexisting condition).

**Results:** The median follow-up was 3.65 years for patients who underwent surgery and 4.29 years for those who did not. Of the 252 women who underwent prophylactic mastectomy, none developed breast cancer. Seventy-five of these women did not undergo prior or concurrent SO. Of the women who did not undergo prophylactic mastectomy, breast cancer developed in 7% (including intraductal disease), which did not seem to vary by BRCA1 versus BRCA2 mutations. SO was associated with a decreased risk of ovarian cancer. For BRCA1 mutations, SO was associated with a hazard ratio (HR) of 0.31 in patients with no prior breast cancer, and the associated HR was 0.15 among patients with a history of breast cancer. After SO in patients with BRCA2 mutations, ovarian cancer did not develop in those without a history of breast cancer, but it developed in 3% of those with a history of breast cancer during 6 years of follow-up. SO reduced the risk of breast cancer recurrences in both BRCA1 (HR, 0.63) and BRCA2 patients (HR, 0.36) without a prior history of breast cancer. SO was associated with a significantly lower overall mortality rate in those who had both no prior breast cancer and those who had prior breast cancer. BRCA1 patients were twice as common as BRCA2 patients, and the survival advantage associated with SO was true for the BRCA1 subgroup.

**Conclusions:** Bilateral mastectomy was effective at reducing the risk of breast cancer development. Even with limited follow-up, SO improved survival.

**Reviewer’s Comments:** For patients with a diagnosis of breast cancer who have had hormones or chemoinduced menopause, SO may not impact the risk of breast cancer. (Reviewer-Jonathan J. Beitler, MD, MBA).

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Keywords: BRCA1 & BRCA2 Mutations, Cancer Risks, Risk Reduction

Print Tag: Refer to original journal article
The Radiation Therapy Oncology Group found that local control at 2 years was 95% with a median survival of 33 months in 70 medically inoperable T1-T2 patients with early NSCLC treated to 60 or 66 Gy in 3 fractions.

**Background:** In this report of stereotactic body radiotherapy (SBRT), “stereotactic” refers to precise 3-dimensional positioning, and “body” is used to distinguish this technique from treatments for the brain and skull base. In contrast to radiosurgery, SBRT requires special evaluation due to target motion because there is an absence of that old reliable surrogate, the skull.

**Objective:** To evaluate SBRT for the treatment of early-stage non-small-cell lung cancer (NSCLC).

**Methods:** A noninvasive body frame system, including a vacuum bag that is fitted at the time of simulation, a scale, an abdominal compression paddle (to restrict abdominal motion), and external fiducial markers are available. Without the body frame, either implanted fiducial markers or in-room volumetric imaging is required for accurate setup. Respiratory gating can be used to account for respiratory motion. Dynamic gating, where the patient is coached to breathe and the beam is only turned on when some predetermined endpoint is reached, is another method. A third method is breath-holding, but this can be particularly difficult in patients with poor pulmonary function. Two commercial systems use fiducial markers implanted into the tumors, and these track the tumor. Chest wall breathing is used most commonly for motion management. It is abdominal compression coupled with instructions for the patient in how they expand their lungs. Chest wall breathing is unnatural but exerts forces in multiple opposing directions as opposed to the up and down of diaphragmatic breathing. Chest wall breathing dampens movement to <1 cm. Conformity index is the ratio of the isodose shell that provides 95% coverage to the PTV volume and should be <1.2. Convolution superposition treatment planning algorithms should be used.

**Results:** The Radiation Therapy Oncology Group (RTOG) found that local control at 2 years was 95% with a median survival of 33 months in 70 medically inoperable T1 and T2 patients treated to 60 or 66 Gy in 3 fractions. Six patients died as a result of toxicity, all with centrally located tumors. One study suggested that there was no significant decline in pulmonary function tests in 15 patients at 1 year after SBRT. The risk of mortality is increased with centrally located tumors.

**Conclusions:** Multiple clinical trials have found that 48 Gy in 4 fractions and 60 to 66 Gy in 3 fractions are biologically effective doses that limit normal tissue reaction.

**Reviewer’s Comments:** The real test comes when T1 operable patients are randomly assigned between surgery and SBRT. The RTOG and the American College of Surgeons Oncology Group are working to make that study a reality. (Reviewer-Jonathan J. Beitler, MD, MBA).

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Keywords: Stereotactic Body Radiotherapy

Print Tag: Refer to original journal article
Metastatic non–small-cell lung cancer patients derive both a significant overall survival benefit and an improved quality of life from early provision of palliative care services.

**Background:** Patients with metastatic non–small-cell lung cancer (NSCL) are frequently referred for palliative care intervention too late to meaningfully affect quality of life (QOL).

**Objective:** To determine the impact of early palliative care intervention on patient-reported outcomes, resource utilization, and QOL for metastatic NSCLC patients.

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

**Participants:** 151 patients who were within 8 weeks of diagnosis of metastatic NSCLC who were recruited at the time of oncology clinic attendance. All participants had an ECOG performance status of 0 to 2.

**Methods:** The Functional Assessment of Cancer Therapy-Lung (FACT-L) scale was used to measure QOL, and the Hospital Anxiety and Depression Scale (HADS) plus the Patient Health Questionnaire 9 (PHQ-9) were used to assess mood. All patients received standard oncologic care. Palliative care specialists (physicians and advanced-practice nurses) met with patients randomized to the palliative care group within 3 weeks of enrollment and monthly to address physical and psychosocial issues including treatment-related decision making and coordination of care.

**Results:** The groups were well balanced for known prognostic factors, and study patients did not differ significantly in demographics or survival compared with eligible unenrolled clinic patients. FACT-L, Lung Cancer Subscale (LCS), and Trial Outcome Index (TOI= LCS plus physical and functional well-being subscales of FACT-L) scores at 12 weeks were all significantly higher for patients in the palliative care group. Significantly fewer palliative care patients had depression at 12 weeks despite equal use of antidepressants in both groups. More control patients than palliative care patients received aggressive end-of-life care. Palliative care patients were more likely to have resuscitation preferences documented in the medical record and had longer median duration of hospice care (11 versus 4 days, difference not significant). The overall median survival was longer in the palliative care group (11.6 months) than in controls (8.9 months, \( P=0.02 \)).

**Conclusions:** Early palliative care intervention improves both survival and QOL for patients with metastatic NSCLC by magnitudes similar to those produced by first-line chemotherapy.

**Reviewer's Comments:** These results quantify the importance of palliative care for patients with metastatic NSCLC. They are probably generalizable to other cancers for patients in the final months of life, providing strong support for the provision of these services in community practice. (Reviewer-Alan B. Grosbach, MD, FACP).

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Keywords: Metastatic NSCL, Early Palliative Care, Quality of Life, Survival

Print Tag: Refer to original journal article
In this retrospective study, high-dose radiation improved survival for patients with Stage III non–small-cell lung cancer with acceptable toxicities.

**Background:** Two things can be done to improve the relatively dismal results of radiation therapy alone for Stage IIIB and medically inoperable Stage IIIA patients with non–small-cell lung cancer (NSCLC). First, the addition of concurrent chemotherapy to good performance patients adds 13% to the 2-year survival rate. Altered dose fractionation is the second “improvement.” The Radiation Therapy Oncology Group and the North Central Cancer Treatment Group have both determined that the maximum tolerated dose is 74 Gy.

**Objective:** To compare the outcomes of high-dose 3D conformal radiation with conventional radiation in patients with Stage III NSCLC.

**Design:** Retrospective single-institution study from Japan.

**Participants:** 100 consecutive patients with inoperable Stage III NSCLC and ECOG performance scores of 0-2 who were treated between 1999 and 2006.

**Methods:** All but 3 patients received platinum-based chemotherapy. The first 33 patients (until 2002) underwent conventional radiation with AP/PA fields and received 56 to 66 Gy. For these patients, the clinical target volume (CTV) was the gross tumor volume (GTV), the ipsilateral hilum, the subcarinal region, both the ipsilateral and contralateral mediastinum, and an additional 5 to 10 mm. The supraclavicular areas were included when the primary tumor was in the upper lobes or main bronchus. The remaining 67 patients had high-dose radiotherapy to 66 to 84 Gy. For these patients, the PTV1 was the primary tumor with 5 to 10 mm margins, and PTV2 was the nodal regions with 5 to 10 mm margins. Typically, PTV1 received 66 Gy, whereas PTV2 received 56 Gy.

**Results:** The 2 groups were well balanced, other than the GTV being larger in the conformal group. The median doses were 60 Gy in the conventional group versus 69.4 Gy in the 3D group. Twenty patients in the 3D group were treated with hyperfractionation (1.2 Gy twice daily) and the remainder received 2 Gy/day. The median overall survival was 13.2 months for the conventionally treated patients and 17.3 months for the 3D patients. Median disease-free survival was 6.2 months for the conventional group and 11.8 months for the 3D group. Likewise, at 2 years, the local progression-free rate was 39.9% for the conventionally treated patients versus 78% for the 3D patients (P<0.05). For the 3D group, the rate of isolated and all elective nodal failure was 4.4% and 6.6%, respectively. Grades 1 and 2 pneumonitis were seen in 54.5% of the conventionally treated patients and in 53.7% of the conformally treated patients. Grade 3 esophagitis was seen in 1 patient in each group.

**Conclusions:** High-dose radiation improved survival with acceptable toxicities.

**Reviewer's Comments:** Phase III studies have yet to prove that high-dose external radiation improves survival rather than just local control. I wish PET/CT had been used for staging and follow-up. (Reviewer-Jonathan J. Beitler, MD, MBA)

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Keywords: Inoperable Stage IIIA and IIIB NSCLC, Radiation Dose

Print Tag: Refer to original journal article
Cancer-Related Fatigue Persists With Methylphenidate

Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Long-Acting Methylphenidate for Cancer-Related Fatigue: North Central Cancer Treatment Group NCCTG-N05C7 Trial.

Moraska AR, Sood A, et al:

J Clin Oncol 2010; 28 (August 10): 3673-3679

Long-acting methylphenidate proved to be ineffective compared with placebo for the treatment of cancer-related fatigue in a phase III trial.

Background: The persistent tiredness that characterizes cancer-related fatigue is an important symptom for most advanced cancer patients. No consistently effective therapy has been identified.

Objective: To determine the effectiveness of long-acting methylphenidate for relieving cancer-related fatigue.

Design: Phase III randomized, double-blind, placebo-controlled trial.

Participants: 148 patients with a cancer-related fatigue score of ≥4 (0-10 subjective scale), and an ECOG performance status of 0 to 2 with a life expectancy of at least 6 months. Diagnoses included breast, colon, prostate, lung, and combination/unknown/other cancers stratified by stage (0-II versus III/IV).

Methods: Patients completed the Brief Fatigue Inventory (BFI) scores weekly and maintained Symptom Experience Diaries to assess adverse events. Short Form-36 (SF-36) Vitality Subscale and Linear Analog Self-Assessment were used to assess quality of life (QOL). The Pittsburgh Sleep Quality Index (PSQI) was used to determine impact on sleep quality. Escalating doses of 18-mg methylphenidate or placebo were administered as 1 tablet daily for the first week, 2 tablets daily for the second week, and 3 tablets daily for the final 2 weeks. The target methylphenidate dose was 54 mg/day.

Results: There was no statistically significant difference between the methylphenidate and placebo groups for "fatigue right now," "usual fatigue," or "worst fatigue." No differences were detected for overall QOL or for individual variables such as fatigue interference with general activity, mood, walking ability, normal work, relations with others, and enjoyment of life. Sleep quality was not enhanced in the methylphenidate group. There was significantly more nervousness and appetite loss among methylphenidate patients despite a lack of overall toxicity differences between the 2 groups and an absence of differences in common symptoms of mild anxiety, dizziness, insomnia, and abdominal pain. Subgroup analyses demonstrated a significant improvement in usual fatigue favoring methylphenidate among patients with stages III and IV cancer (P=0.02), but this difference was reversed, favoring placebo patients among those with early cancers (stages 0 to II).

Conclusions: Methylphenidate at a dose of 54 mg/day is not an effective treatment for cancer-related fatigue.

Reviewer's Comments: The authors point out that the long-acting methylphenidate preparation used in this study may be less suitable for treating cancer-related fatigue than a short-acting multiple-dose formulation. A shorter duration of action would likely be associated with higher peak levels and possibly greater benefit. Whether it would also result in more side effects is uncertain. (Reviewer-Alan B. Grosbach, MD, FACP).

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Keywords: Cancer-Related Fatigue, Long-Acting Methylphenidate

Print Tag: Refer to original journal article
Patients with primary carcinoma in situ (CIS) of the urinary bladder have a worse outcome than do patients with secondary CIS (associated with papillary tumors).

**Background:** Primary bladder carcinoma in situ (CIS) is defined as isolated CIS with no prior or concomitant papillary tumors. Secondary bladder CIS is defined as CIS which occurs concomitantly with or after a papillary bladder tumor.

**Objective:** To determine differences in clinical outcomes in patients with primary versus secondary bladder CIS.

**Design:** Retrospective review.

**Methods:** Of 476 patients with bladder CIS, 221 had primary CIS and 255 had secondary CIS. All patients were initially treated with transurethral bladder tumor resection and/or biopsy, and all received intravesical bacillus Calmette-Guérin (BCG) therapy. Time to progression of invasive disease (T1) and time to progression to muscle invasive disease were analyzed.

**Results:** Patients with primary bladder CIS responded better within 6 months to BCG therapy than did those with secondary CIS. The 5-year cumulative incidence of progression to T1 or higher bladder cancer was 43% in the primary group versus 32% in the secondary group. Progression to muscle invasive disease occurred in 17% of patients with primary CIS versus 8% of patients with secondary CIS. Both of these differences were statistically significant. The median follow-up for this study was 5 years.

**Conclusions:** Patients with primary bladder CIS have a worse outcome than those with secondary bladder CIS.

**Reviewer’s Comments:** The authors of this interesting paper suggest that patients who present with CIS without concomitant papillary tumors fare worse than patients who present with both papillary tumors and CIS. Interestingly, gross hematuria was more often seen in the secondary group while irritative or obstructive voiding symptoms were more commonly seen in patients with primary CIS. Neither of these findings is surprising, but it is nice to have them documented. The bottom line is that primary CIS appears to carry a worse prognosis than secondary CIS and, as the authors suggest, these 2 tumor types may be different. I guess one could argue that, although these 2 disease entities may be different, it may not matter in clinical practice. The presence of CIS, whether it is primary or secondary, is treated with BCG, and radical cystectomy is reserved for BCG failures. On the other hand, primary CIS may be a more aggressive disease, and understanding the differences between primary CIS and CIS which occurs in the presence of a papillary tumor may significantly improve our understanding of the pathophysiology of bladder cancer. In summary, it appears that not all CISs of the urinary bladder are the same disease process. (Reviewer-George S. Benson, MD).
Statin Use Reduces Risk of Prostate Cancer Diagnosis

*The Association Between Statin Use and the Diagnosis of Prostate Cancer in a Population Based Cohort.*
Breau RH, Karnes RJ, et al:
J Urol 2010; 184 (August): 494-500

In this study by Breau and colleagues, the use of statins was shown to be associated with a decreased incidence in the diagnosis of prostate cancer.

**Objective:** To determine the effect of statin use on the risk of prostate cancer.
**Methods:** A population-based cohort of 2447 men (age range, 40-79 years) was analyzed. These men had been followed up from 1990 to 2007. Questionnaires were completed every 2 years, and information on statin use was self-reported. A randomly selected subset of 634 men completed urologic examinations that included a prostate-specific antigen (PSA) determination every 2 years. Prostate cancer diagnosis and the performance of a prostate biopsy were determined by reviewing medical records.
**Results:** Prostate cancer was diagnosed in 6% of statin users versus 10% of non-statin users. Statin use was also associated with a decreased risk of undergoing prostate biopsy and a decreased risk of the finding of prostate cancer. Statin use was also associated with a decreased risk of having a PSA level >4.0 ng/mL, although this finding was not statistically significant. Finally, a longer duration of statin use was associated with a lower risk of having a diagnosis of prostate cancer.
**Conclusions:** The authors believe that statin use is associated with a decreased risk of a prostate cancer diagnosis.

**Reviewer’s Comments:** Several observational studies examining statin use and the risk of prostate cancer have been published and have shown contradictory results. Statins not only reduce cholesterol levels and prevent cardiovascular events, but they have also been shown to induce apoptosis and arrest growth in prostate cancer cell lines. In addition, statins may reduce serum PSA levels. The results of this study appear to demonstrate that statin users have a lower risk of having a diagnosis of prostate cancer, but there are significant problems with analyzing these results. First of all, in this study, statin users were older and more likely to also be taking NSAIDs and 5α-reductase inhibitors. In addition, the non-statin users had higher PSA levels at baseline. The imbalance in baseline PSA levels alone might explain the higher rates of prostate biopsy and subsequent diagnosis of prostate cancer in the non-statin user group. In summary, some in vitro data show that statins have antineoplastic effects in prostate cancer cell lines. Observational studies examining statin use and the risk of prostate cancer have shown contradictory findings. In addition, statins may reduce serum PSA levels. In my opinion, we are still a long way from determining that statin use in some way is protective for the development of prostate cancer. (Reviewer-George S. Benson, MD).

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Keywords: Prostate Cancer Risk, Effect of Statins

Print Tag: Refer to original journal article
Single-agent arsenic trioxide treatment of patients with acute promyelocytic leukemia produced a single-institution complete remission rate of 86% and a 5-year survival rate of 74%.

**Background:** Arsenic trioxide (ATO) is a highly active single agent for inducing remissions in patients with acute promyelocytic leukemia (APL), but the durability of these remissions has been questioned.

**Objective:** To report long-term follow-up on a series of APL patients following remission induction with ATO.

**Design:** Prospective, single-institution, single-arm trial.

**Participants:** 72 patients with newly diagnosed APL in whom treatment was initiated between 1998 and 2004. Fifteen patients were aged ≤15 years, and in this pediatric cohort, the median age was 13 years (age range, 3-15 years).

**Methods:** Platelet transfusions were given for counts lower than 20,000. No ECG monitoring was performed during ATO infusions or on follow-up. Single-agent ATO comprised induction, consolidation, and maintenance therapy, except for 1 to 2 doses of anthracycline during induction at the attending physician's discretion for poorly resolving differentiation syndrome, for initial WBC >50,000, or for rapidly rising WBC despite hydroxyurea.

**Results:** 62 of 72 patients (86%) achieved complete remission (CR), with 7 deaths within the first week (all from intracranial bleeds) and 3 deaths during weeks 3 to 7 (1 intracranial bleed, 1 sepsis, 1 differentiation syndrome). During induction, 8 patients received anthracycline, and 53 received hydroxyurea. Of 62 CR patients, 13 relapsed, including 2 good-risk patients (initial WBC <5,000) and 11 high-risk patients (initial WBC >5,000). Relapses occurred at a median of 1.5 years (5 relapses at >2 years; 2 relapses at >4 years). At 5 years, the overall survival rate was 74.2%, the event-free survival rate was 69%, and the disease-free survival rate was 80%. Hepatotoxicity manifested by enzyme elevation was observed in 24 patients, including 5 with grade 3/4 toxicity that required ATO discontinuation for 1 to 4 weeks. Homozygosity for the mutant methylenetetrahydrofolate reductase gene A1298C was associated with an increased hepatotoxicity risk (RR, 3.5). Patients who developed hepatotoxicity had a lower relapse rate (2 of 23 patients) than those who did not (11 of 39 patients), but the difference in relative risk was not significant (RR, 4.1; P=0.08). In their discussion, the authors point out that their high-risk patients experienced more relapses than expected with conventional chemotherapy. This includes the 5 late relapses that occurred after 2 years.

**Conclusions:** Single-agent arsenic trioxide treatment is a reasonable option for good-risk APL patients.

**Reviewer’s Comments:** These are provocative results, but single-agent ATO is unlikely to be adopted as standard therapy for most APL patients. (Reviewer-Alan B. Grosbach, MD, FACP).

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Keywords: Acute Promyelocytic Leukemia, Remission Induction, Arsenic Trioxide

Print Tag: Refer to original journal article
Early HL Outcomes Not Improved With Dose Escalation

*Intensified Chemotherapy and Dose-Reduced Involved-Field Radiotherapy in Patients With Early Unfavorable Hodgkin’s Lymphoma: Final Analysis of the German Hodgkin Study Group HD11 Trial.*

Eich HT, Diehl V, et al:

J Clin Oncol 2010; 28 (September 20): 4199-4206

Four cycles of ABVD with 30 Gy of involved field radiation (IFRT) leads to equivalent results in patients with early unfavorable Hodgkin lymphoma compared with 4 cycles of BEACOPP followed by either 30 or 20Gy of IFRT.

**Background:** Early stage unfavorable Hodgkin lymphoma (HL) is conventionally treated with chemotherapy (generally ABVD for 4-6 cycles) and involved field radiation (IFRT) to doses of 30 to 36 Gy.

**Objective:** The German Hodgkin Study Group (GHSG) wanted to investigate intensification using BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) and to evaluate the non-inferiority of 20 Gy versus 30 Gy IFRT following chemotherapy.

**Design:** Prospective randomized 2x2 trial.

**Participants:** Patients had stage IA, IB, or IIA HL with at least 1 risk factor: (1) bulky mediastinal mass more than 1/3 maximum transverse diameter, (2) extranodal involvement, (3) erythrocyte sedimentation rate (ESR) ≥50 mm/h or ≥30 mm/h in patients with B symptoms, or (4) ≥3 involved lymph nodes neither bulky mediastinal disease nor extranodal involvement was present.

**Methods:** Patients were randomly assigned to ABVD x 4 or BEACOPP x 4 followed by either 20 Gy or 30 Gy of IFRT. The primary endpoint was freedom from treatment failure.

**Results:** From 1998 to 2003, 1395 eligible patients were enrolled, and 94% had stage II disease. Patients received a mean relative chemotherapy dose intensity of 91.7% for ABVD and 94.7% for BEACOPP. Treatment toxicities were more common for ABVD, but patients receiving BEACOPP more often developed severe toxicities, such as hematologic toxicities and hair loss. Only 3% of patients had a 10% deviation in their radiation, and 12% of 30-Gy patients versus 5.7% for 20-Gy patients developed grade 3 or 4 toxicities, most commonly dysphagia and mucositis. With a mean follow-up of 82 months, there were 52 secondary neoplasms, with no differences between groups. The 2 groups did not differ in survival. The overall complete response rate was 94.1%, and with a median follow-up of 82 months, the relapse rate was 9.7%. After 4 cycles of BEACOPP, 20 Gy was non-inferior to 30 Gy in Freedom from Tumor Failure (FFTF), but after 4 cycles of ABVD, a >7% difference in FFTF could not be excluded as the 5-year difference was 4.7%.

**Conclusions:** Four cycles of ABVD with 30 Gy of IFRT leads to equivalent results compared with four cycles of BEACOPP followed by either 30 or 20 Gy of IFRT. Four cycles of ABVD followed by 20 Gy of IFRT was inferior to the other 3 arms, implying that a reduction of IFRT dose from 30 to 20 Gy is only possible with the more toxic BEACOPP.

**Reviewer’s Comments:** Pick your poison: more toxic chemotherapy or higher doses of radiation. Concepts brought up by the authors were reduced fields of radiation so that the treatments were not to an entire nodal area but to initially involved nodes (with a margin). The authors also brought up how to incorporate a PET-defined CR after initial chemotherapy. (Reviewer-Jonathan J. Beitler, MD, MBA).

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Keywords: Early Stage Unfavorable Disease,

Print Tag: Refer to original journal article
Intensive Chemotherapy Does Not Benefit Most Older Patients (Age 70 Years or Older) With Acute Myeloid Leukemia.

Kantarjian H, Ravandi F, et al:

Blood 2010; July 28 (): epub ahead of print

Nearly 75% of patients with acute myeloid leukemia aged ≥70 years had low rates of complete remission and 8-week mortality rates in excess of 30% when treated with intensive chemotherapy.

Background: Because of suboptimal response to therapy and poor overall prognosis, patients aged >70 years with acute myeloid leukemia (AML) derive little benefit from intensive chemotherapy. Which subsets of these patients would benefit from intensive chemotherapy and the degree of benefit are unknown.

Objective: To identify patients unlikely to benefit from intensive chemotherapy for AML due to excessive 8-week mortality rates.

Design: Retrospective single-institution experience.

Participants: 446 patients with AML (≥20% blasts) whose ages ranged from 70 to 88 years and were treated between 1990 and 2008. In the population studied, 13% were aged ≥80 years.

Methods: Deaths during the first 8 weeks were defined as induction mortalities. All patients received either high-dose (98%) or standard-dose (2%) cytarabine. In addition, 96% of patients received 1 or 2 additional agents, including idarubicin, fludarabine, topotecan, cyclophosphamide, and clofarabine.

Results: Among 430 patients negative for Core Binding Factor (CBF) leukemia, the complete remission (CR) rate was 45% and the 8-week mortality rate was 36%. Median duration of CR was 10.8 months, and the median survival of CR patients was 13.8 months. Among CBF leukemia patients, 10 of 16 achieved CR (63%), with the median CR duration being 12 months, the median survival being 15 months, and the 8-week mortality rate being 21%. Multivariate analysis identified the following factors as independently associated with adverse 8-week survival: age ≥80 years, ECOG performance status 2-4, complex karyotype, and creatinine >1.3 mg/dL. When the 430 CBF-negative patients were subdivided according to 0, 1, 2, and >3 of these factors, CR rates in the 4 groups were 57%, 52%, 29%, and 16%, respectively. The 8-week mortality rate in the 4 groups was 16%, 31%, 55%, and 71%, respectively. Median survival duration and 2-year and 3-year survival rates were 11.3 months, 30%, and 22% for CBF-negative patients with 0 risk factors; were 5.3 months, 15%, and 7% with 1 risk factor; were 1.5 months, 7%, and 6% with 2 risk factors; and were 0.5 months, 0%, and 0% with >3 risk factors. The validity of these groupings was confirmed.

Conclusions: Intensive chemotherapy is potentially appropriate for AML patients aged ≥70 years who have none of the adverse risk factors identified in this study (28% of the study population). Patients in the higher risk groups (72% of the study population) with high rates of early death and poor CR rates should be considered for lower intensity investigational treatment.

Reviewer's Comments: These results underscore the importance of thoughtful individualization of treatment for 70-plus-year-olds with AML. Lower intensity regimens and investigational trial enrollment are the best options for most such patients. (Reviewer-Alan B. Grosbach, MD, FACP).

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Keywords: Elderly Patients, Intensive Chemotherapy, Outcomes

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Histopathologic response to preoperative therapy was associated with a significantly improved disease-specific survival in patients with high-grade retroperitoneal sarcoma.

**Objective:** To determine the impact of histopathologic response on disease-specific survival (DSS) after preoperative adjuvant therapy for high-grade retroperitoneal sarcoma.

**Design:** Retrospective single-institution study.

**Participants:** 55 patients with high-grade primary retroperitoneal sarcomas who underwent preoperative chemotherapy with or without radiation therapy.

**Methods:** Chemotherapy included doxorubicin, dacarbazine or gemcitabine/docetaxel, and ifosfamide-based regimens. All patients received radiation therapy as external beam with a total dose of 50 Gy. However, not all patients received preoperative radiation therapy. Histopathological responders were defined as ≥95% pathologic necrosis. DSS rates were compared between responders and nonresponders.

**Results:** All patients underwent complete surgical resection. The median age was 56 years, and about 40% of patients in the study were female. Fourteen patients (25%) had >95% histopathologic necrosis. The median amount of tumor necrosis was 50%. Median tumor size was 15 cm. There was not a significant difference in the percentage of patients treated with preoperative radiation therapy among responders and nonresponders. Response rates were significantly lower for patients with leiomyosarcomas as compared with other histologies. The 5-year DSS for all patients was 47% (responders, 83%; nonresponders, 34%; \( P = 0.002 \)). On multivariate analysis, histopathologic response and young age were significantly associated with DSS. The response rate was a better predictor of DSS as compared to the Memorial Sloan-Kettering Cancer Center sarcoma nomogram, which includes tumor size, depth, site, histology, age, and grade.

**Conclusions:** Histopathologic response to preoperative therapy was associated with a significantly improved DSS.

**Reviewer’s Comments:** The DSS rate for patients with high-grade retroperitoneal sarcoma remains poor despite complete surgical resection. Randomized multicenter studies evaluating optimal strategies for these difficult malignancies are lacking. (Reviewer-Todd M. Tuttle, MD).
Objective: To determine the outcomes of patients with peritoneal metastases from gastric cancer treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy (PIC).

Design: Retrospective multicenter study.

Participants: 159 patients from 15 participating institutions that treated patients with peritoneal metastases from gastric cancer using cytoreductive surgery plus PIC. Peritoneal metastases were confirmed on pathology in all patients. All patients received treatment with hyperthermic intraperitoneal chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), or both within 7 days of surgery. Patients with extra-abdominal metastases were excluded.

Results: Women comprised about 50% of the study population, and the mean patient age was 53 years. The gastric cancers were well differentiated (20%), moderately differentiated (22.5%), or poorly differentiated (57.5%). After cytoreductive surgery, 56% of patients had no residual macroscopic disease, 25% had residual disease <2.5 mm, and 19% had residual disease >2.5 mm. Most patients (94%) received HIPEC, and 7.5% received EPIC. Various drugs were used for PIC. The postoperative mortality rate was 6.5%. Major complications (grade 3-4) occurred in 28% of patients, and the reoperation rate was 14%. Age older than 60 years was significantly associated with a higher complication rate. The 1-year, 3-year, and 5-year survival rates were 43%, 18%, and 13%, respectively. The disease-free survival rate was only 12% at 3 years. On multivariate analysis, institution and completeness of cytoreduction were significantly associated with survival.

Conclusions: Cytoreductive surgery plus intraperitoneal chemotherapy may achieve long-term survival in selected patients with peritoneal metastases from gastric cancer.

Reviewer's Comments: The morbidity and cost of this treatment for gastric cancer patients is very high. Very strict selection criteria (young age, favorable histology, ability to resect all disease) should be applied. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Gastric Cancer, Peritoneal Metastases, Cytoreductive Surgery, Intraperitoneal Chemotherapy

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Survival Differs for Stage IV Prostate Cancer Subtypes

Stage IV Prostate Cancer: Survival Differences in Clinical T4, Nodal and Metastatic Disease.

Hsiao W, Moses KA, et al:

J Urol 2010; 184 (August): 512-518

Men with T4N0M0 (locally advanced) prostate cancer have a better prognosis than do men with metastatic (TxNxM1) prostate cancer.

**Background:** Currently, stage IV prostate cancer consists of a heterogeneous group. Specifically, stage IV disease consists of locally advanced disease, nodal disease, and metastatic disease.  

**Objective:** To determine the patient outcomes associated with the various subtypes of stage IV prostate cancer.  

**Methods:** 17 registries were queried in the Surveillance, Epidemiology and End Results (SEER) program. The overall survival and prostate-cancer–specific survival were determined across the 3 subtypes of stage IV prostate cancer.  

**Results:** 615 patients had T4N0M0 disease, 3200 had TxN1M0 disease, and 11,000 had TxNxM1 disease. Across all age ranges, patients with M1 disease (metastatic disease) fared worst. In all patients, those with T4 disease (locally advanced disease) fared worse than those with N1 disease. Importantly, younger patients (age <50 years) with locally advanced cancer did well after surgery, and their survival rates were significantly higher than that for patients with either N1 or M1 disease. Other factors also had a significant association with poor survival, including high tumor grade, unknown tumor grade, and absence of a spouse.  

**Conclusions:** Not all subtypes of stage IV prostate cancers behave the same. Of note, young men with locally advanced (T4) disease tend to do well following surgery.  

**Reviewer’s Comments:** This paper clearly shows that not all patients with stage IV prostate cancer defined by the TNM staging system have the same outcome. Although all are classified as stage IV disease, patients with either locally advanced or nodal disease have better overall survival than do patients with metastatic disease. The most interesting finding in this study is that young men (age <50 years) with locally advanced (T4) disease tend to do very well after surgery. This paper is convincing in that not all stage IV prostate cancers are the same. (Reviewer-George S. Benson, MD).

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Keywords: Stage IV Prostate Cancer, Subtypes vs Outcomes

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Radical transurethral resection of muscle invasive bladder tumors may be an alternative to radical cystectomy in selected patients.

**Objective:** To determine the results of radical transurethral resection of bladder tumor (TURBT) in selected patients with muscle-invasive bladder cancer (MIBC) who were followed up for >15 years.

**Design/Participants:** Nonrandomized, noncomparative trial of 133 patients who had MIBC and underwent complete TURBT.

**Methods:** All patients had negative biopsies of the tumor bed. Patients with positive biopsies, hydronephrosis, or metastases were excluded. The minimum follow-up was 15 years.

**Results:** At 5, 10, and 15 years, the cancer-specific survival rate was 82%, 80%, and 77%, respectively, and the progression-free survival rate with bladder preservation was 76%, 65%, and 58%, respectively. Progression and recurrence occurred primarily during the first 3 years.

**Conclusions:** Radical transurethral bladder tumor resection is reasonable therapy for selected patients with muscle-invasive bladder cancer. If the bladder tumor can be completely resected and if biopsies of the tumor bed are negative, then the authors recommend this approach in selected patients.

**Reviewer’s Comments:** Periodically, papers advocating radical transurethral resection rather than radical cystectomy for MIBC appear in the literature. The cancer-specific survival rates and progression-free survival rates in this study are very good and are comparable to those seen in radical cystectomy series. On the other hand, the results of this paper are somewhat difficult to analyze because all patients were “selected.” There was no control group. The study necessary to prove the beneficial effects of radical TURBT would be a randomized trial to either radical TURBT or radical cystectomy. I doubt that this study will ever be undertaken. Perhaps there is a group of patients who can be adequately managed with radical transurethral resection of their muscle-invasive bladder tumor. For the foreseeable future, however, I think that radical cystectomy will remain the treatment of choice for MIBC. (Reviewer-George S. Benson, MD).

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Keywords: Muscle Invasive Bladder Cancer, Radical Transurethral Resection, Outcomes

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