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Ascites, Neoadjuvant Chemotherapy, and Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: This study performed a retrospective analysis of ovarian cancer patients and found that residual tumor and volume of ascites were independent prognostic factors. They then performed a prospective, nonrandomized phase II study comparing primary surgery with neoadjuvant chemotherapy in patients with large volume ascites (> 500 cc). Their results suggest an improved survival rate if neoadjuvant chemotherapy is given to these patients.

Source: Kuhn W, et al. *Cancer*. 2001;92:2585-2591.

From 1996 to 2000, 31 patients with laparoscopically diagnosed stage IIIC ovarian cancer with large volume ascites (> 500 cc) were enrolled in a study of neoadjuvant chemotherapy. Treatment consisted of 3 preoperative cycles of carboplatin (AUC = 5) and paclitaxel (175 mg/m^2), and 3 additional cycles postoperatively. Those considered to be "in poor general health" had the paclitaxel omitted.

A control group consisted of 32 comparable patients treated with surgery followed by 6 cycles of chemotherapy during the same time period. These patients had either refused entry onto the protocol or did not appear "compatible for psychological reasons." In this prospective, but nonrandomized, analysis, Kuhn and colleagues found that neoadjuvant therapy improved the median survival for patients with large volume ascites (42 vs 23 months, $P = 0.0007$).

COMMENT BY KENNETH W. KOTZ, MD

Over the years, as survival in ovarian cancer was highly dependent on optimal cytoreduction, the standard of care has been aggressive surgical debulking followed by chemotherapy. The theoretical advantage of this approach includes improved chemosensitivity because large necrotic tumors with marginal blood supply have been removed leaving behind the smaller residual tumors with a higher growth fraction.

INSIDE

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Patients with large volume ascites are less amenable to optimal primary cytoreduction and may have a worse prognosis. A retrospective, multivariate analysis was performed on 193 stage IIIC ovarian cancer patients treated between 1982 and 1995. Kuhn et al found that postoperative residual tumor (> 2 cm) had the strongest effect on prognosis, but that the volume of ascites was also an independent prognostic factor. For example, patients with > 500 cc ascites had a median survival of 19 months compared to 53 months for patients with < 500 cc.

The subsequent prospective analysis of these higher-risk patients with large-volume ascites showed that suboptimal debulking (> 2 cm residual) occurred less often in patients treated with neoadjuvant chemotherapy (16% vs 37%; $P = 0.04$). Of greater importance, however, is that the neoadjuvant chemotherapy was associated with a survival advantage (median survival, 42 vs 23 months). No difference in surgical morbidity or mortality emerged.

Even though the 2 prospectively studied groups were well balanced with respect to age, histology, grade, and lymph node status, bias may have been introduced by the lack of randomization. Specifically, the exclusion of patients not appearing psychologically fit might have shifted sicker patients into the control group. In addition, Kuhn et al point out that a bias toward more aggressive debulking could have occurred in patients treated with preoperative chemotherapy. Whether the 2 groups were balanced with respect to the omission of paclitaxel and delivery of planned chemotherapy was not reported.

Even in the platinum/paclitaxel era, the proportion of patients with stage III/IV disease who undergo maximal cytoreduction remains one of the most important predictors of survival.[1] Interval cytoreductive surgery has also been shown to improve survival for patients in whom the primary surgery resulted in suboptimally debulked disease.[2,3] Therefore, the improved survival from neoadjuvant therapy noted by Kuhn et al may be the result of improved resectability after downstaging. In fact, a multivariate analysis by Kuhn et al showed that residual tumor, but not timing of chemotherapy, had a statistically significant prognostic value. Unfortunately, Kuhn et al did not report response rates or results of serum tumor markers.

Neoadjuvant therapy may also be appropriate to reduce surgical morbidity. Lower postoperative mortality rates,[4] as well as shorter surgical time and fewer transfusions,[5,6] have been reported with neoadjuvant therapy. Higher-risk patients in whom surgery might be delayed in order to institute chemotherapy include those with uncountable plaques, tumor load > 1 gm, a poor performance status,[4] poor nutritional status, or stage IV disease (excluding pleural effusion).[4,6] Those not responding to chemotherapy could be identified and approached more palliatively.

To summarize, neoadjuvant chemotherapy may be useful to reduce surgical morbidity in certain high-risk patients. In patients with large-volume ascites, the results of Kuhn et al suggest, but do not prove, that there may even be a survival advantage. The applicability of this approach to other patients with ovarian cancer is unknown, but does not seem to be associated with a worse outcome.[4,6] ❖

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Clinical Staging and Chemoradiation for Early Stage Hodgkin's Disease

ABSTRACT & COMMENTARY

Synopsis: There is no uniform standard for treating early stage Hodgkin's disease, the most curable form of the disease. Pathologic staging, including exploratory laparotomy and splenectomy, may precede subtotal lymphoid irradiation (STLI), but can entail morbidity without a proven survival benefit. SWOG and the CALGB recently completed an intergroup trial comparing outcomes for clinically staged patients treated with either STLI vs. adriamycin/vinblastine followed by STLI in an effort to determine whether patholgic staging can be abandoned in early stage patients without harming cure rates.

Source: Press O, et al. *J Clin Oncol*. 2001;19: 4238-4244.

Laparotomy for staging of hodgkin's disease was introduced in the 1960s, and is responsible for upstaging 20-30% of patients by detecting occult subdiaphragmatic disease. Splenectomy is typically part of the procedure. Patients without subdiaphragmatic disease may be managed with subtotal lymphoid irradiation, and achieve 10-year disease-free survival rates of 70-80%. Nevertheless, critics of this approach cite morbidity stemming from laparotomy/splenectomy, potential for second malignancies related to radiotherapy, and potential cardiotoxicity linked to radiotherapy as factors which, if improved, may lead to better outcomes.

Press and colleagues reported positive results for their SWOG 9133/CALGB 9391 intergroup phase III randomized trial. In this study, they hypothesized that a "short course of limited chemotherapy" might improve disease-free or overall survival compared with standard STLI while sparing patients the necessity of a laparotomy/splenectomy. Eligible patients had no prior history of laparotomy, radiotherapy or chemotherapy, nonbulky disease, no B symptoms, and no serious comorbidities. Pregnant or lactating females were not eligible. Staging with CT chest/abdomen/pelvis, bone marrow biopsy, and bloodwork including LDH was mandatory. Further staging with gallium scan, lymphangiogram (LAG), and PET scan were strongly recommended but not required. Patients with disease below the diaphragm were excluded.

Press et al eliminated MOPP chemotherapy from consideration for the protocol because of its known toxicities. The other accepted combination regimen, ABVD, was also felt to be too toxic for patients with early stage disease. Press et al bypassed the pulmonary toxicity seen with bleomycin, and the phlebitis and nausea associated with dacarbazine, by paring ABVD to AV, using only adriamycin and vinblastine. Adriamycin was administered intravenously at 25 mg/m^2 and vinblastine i.v. at 6 mg/m^2 on days 1 and 15, these were done in 3 28-day cycles preceding radiotherapy in the combined modality arm. A 6-week break was built into the protocol prior to starting STLI so that interactions between adriamycin and RT might be minimized. Patients were restaged at the completion of chemotherapy.

The trial was opened in 1989 with an accrual target of 420 patients. Patients were stratified by age (< 35, > 35), sex, number of involved sites, histology, presence of high-neck disease, and use of a lymphangiogram for staging. Pathology slides were centrally reviewed. By the time the study was prematurely closed for accrual in April 2000, 348 patients had been randomized to STLI alone vs. combined chemotherapy followed by STLI (combined modality therapy, [CMT]). Radiotherapy parameters were centrally reviewed at the start of RT. STLI was given at 1.8-2 Gy per fraction for 20 fractions for a total dose of 36-40 Gy with 4-10 MV photons. Mantle and paraaortic/spleen fields were treated sequentially.

Median age was 32 years (r, 17-85). Median follow-up was 3.3 years (r, N/A). There was a slight male preponderance. Two thirds of patients in each arm had disease in > 2 lymph nodes. An unspecified number of patients had no residual measurable disease following biopsy. Eighty percent of patients in each arm had nodular sclerosing or lymphocyte predominant histologies. One quarter of the study population underwent LAG. Overall, the 2 study arms demonstrated comparable demographics.

The 2 planned interim analyses were performed on an intention-to-treat basis. Of the 348 patients enrolled, 22 were ineligible for evaluation, leaving 161 in the STLI arm and 165 in the CMT arm. Seven patients were not treated according to their random-

ization, and 9 did not complete their courses of therapy. Overall, there were 295 fully assessable patients (85%), including 147 in the STLI arm and 148 in the CMT arm. The estimated 3-year disease-free survival was 81% in the STLI arm, and 94% in the CMT arm ($P < .001$). Overall survival was not significantly different between arms. There was 1 treatment-related death in each arm, with 6 more deaths in the STLI arm (4.3%) and 3 more deaths in the CMT arm (1.8%) (P = NS). There were significantly more Grade 3 and 4 toxicities in the CMT arm ($P = .004$). Among the 31 relapsed patients in the STLI arm, 12 (39%) relapsed in-field. Among the 9 relapsed CMT patients, 4 (44%) relapsed in-field.

Press et al reported that SWOG and CALGB closed their study early once the second interim analysis results were completed. They based their decision on what they felt was the markedly superior disease-free survival rate observed in the CMT arm. They concluded that their trial, the largest American study of early stage Hodgkin's disease to date, decisively demonstrated that pathologic staging can be sacrificed while maintaining excellent disease-free and overall survival. They stated that this trial conclusively demonstrated that adriamycin/vinblastine + STLI is well tolerated, and confers a superior DFS rate in comparison to STLI alone for stages IA and IIA Hodgkin's disease with minimal toxicities.

COMMENT BY EDWARD J. KAPLAN, MD

Press et al discussed 3 cons related to radiotherapy at the beginning of their report, and those were the incentive to perhaps find a better way. Those were: morbidity from laparotomy/splenectomy; second primary tumors caused by RT; and cardiac toxicity caused by RT. Their protocol schema addressed only the first of these issues.

One question that comes to mind immediately is whether there was selection bias favoring the CMT arm. Usually, patients who receive STLI do so after they have been pathologically staged. This was not the case in the SWOG trial. It is likely that 20-30% of the STLI patients had occult subdiaphragmatic disease, and ordinarily would not have been treated with STLI alone. Furthermore, while PET scan staging was recommended, we are not given details about whether such scanning was equitably distributed between the 2 arms. We do know that patients were stratified by LAG, but not by PET. While total lymphoid irradiation covers the mantle and inverted-Y fields, including the entire spleen if intact, STLI omits the pelvis, and PET scanning can be useful for demonstrating disease in the pelvis as well as elsewhere. In addition, it is unclear what, if anything, was done with the restaging information obtained after CMT patients completed their chemotherapy.

In examining the data presented by Press et al, they indicated that 99 patients (34%) had responses that were either unconfirmed or not assessable. They then stated that there was a significant difference in the overall response rate favoring the CMT arm (P =.004) without disclosing their denominator. Press et al go on to rationalize the lack of difference in overall survival between arms by suggesting that it is a reflection of the success of second-line salvage therapies. However, no data at all were presented in that regard.

Press et al stated that "our analysis suggests that relapses are diminished both within and outside the irradiated field." Despite this assertion, their results do not support their contention. While 39% of relapses in the STLI arm were in-field, 44% in the CMT arm were in-field. P values were not provided.

While I agree with the goals of the study, its design seems to have a built-in handicap for the STLI arm based on the use of clinical staging. Perhaps if all patients underwent PET scan evaluation first, omitting surgery might not be as important an issue.[1,2] Alternatively, the trial could have compared pathologically staged patients treated with STLI to clinically staged patients treated with chemoradiation. Of course, few studies with a surgical and nonsurgical arm have been completed.

Some radiation oncologists would suggest that the doses of radiation used in the trial were too high. A recently published randomized trial from Europe compared 30 Gy to 40 Gy for treating uninvolved nodal areas, and found no difference in DFS with the use of lower doses.[3] Many clinicians feel that 30 Gy is an appropriate dose for involved or uninvolved areas. Certainly, lower doses would lower toxicities.

Press et al are right in adding that further follow-up is necessary before survival, relapse, and salvage patterns are known. It should also be borne in mind that, as Hoppe from Stanford has pointed out, complications of therapy can take more than 15 years to manifest.[4] The addition of adriamycin to STLI may lead to increased cardiac toxicity far off in the future, possibly lowering overall survival, and thereby rendering a combined modality approach less attractive. ❖

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Tamoxifen and Breast Cancer Incidence Among Women with Inherited Mutations in BRCA1 and BRCA2

ABSTRACT & COMMENTARY

Synopsis: While increasingly individualized cancer treatment protocols are gaining prominence due to potentially improved efficacy, directed prevention such as that examined in the phase III Breast Cancer Prevention Trial (BCPT) may be effective on a broader scale. In order to identify whether the tamoxifen benefit realized by high-risk women in the BCPT extended to those at even higher risk, women with BRCA1 and BRCA2 mutations were studied. Genomic analysis was performed on the 288 women in the BCPT trial who developed breast cancer, identifying 19 with BRCA1 or BRCA2 mutations. This subgroup was analyzed for tamoxifen vs. placebo use and presence of tumor estrogen receptor (ER) positivity. Although statistical significance was not achieved, preventative tamoxifen appeared to confer a risk reduction of 62% (95% confidence interval, 0.06-1.56) in BRCA2 mutation carriers and appeared to confer no risk reduction in the small number of BRCA1 mutation carriers. Only 14.2% of BRCA1 carriers were ER-positive, while 66.7% of BRCA2 carriers were ER-positive.

Source: King M-C, et al. *JAMA*. 2001;286:2251-2256.

In 1998, a randomized clinical trial of the National Surgical Adjuvant Breast and Bowel Project, the Breast Cancer Prevention Trial (BCPT) (P-1), revealed that tamoxifen conferred a protective effect for women at high risk for breast cancer.[1] Study subjects were selected for age > 60 years, age < 60 years with a 5-year predicted risk for breast cancer of at least 1.66%, or a history of lobular carcinoma in situ. After subjects had ingested placebo or 20 mg tamoxifen daily for 5 years, a risk reduction of 49% overall was identified among the tamoxifen group. Notably, tamoxifen reduced the incidence of estrogen receptor-positive (ER+) tumors by 69%, although there was no reduction in the risk of estrogen receptor-negative (ER-) tumors.

Given these data, King and colleagues hypothesized that women with germline mutations of BRCA1 or BRCA2 tumor suppressor genes could potentially derive even greater benefit from chemical prevention, given their lifetime breast cancer risk of greater than 80%.[2] The general BCPT null hypothesis that tamoxifen confers no protective benefit is also applicable to cases (women diagnosed with breast cancer) only. Moreover, the same null hypothesis (no tamoxifen benefit) applies to women with cancer (cases) both with and without BRCA mutations. Therefore, if tamoxifen use yielded no benefit, the number of women with cancer and BRCA1 or BRCA2 mutations who used tamoxifen should equal the number of those who used placebo.

In this case-only study, King et al identified BCPT participants who had been diagnosed with an incident invasive breast cancer between June 1, 1992 (start of the BCPT) and September 30, 1999. Follow-up information was available for 13,195 of the original 13,388 participants. Complete 3-year follow-up was available for 80% of participants; complete 5-year follow-up was available for 65% of participants. Median follow-up was 5.7 years. Among the 13,195 patients with follow-up, 320 were diagnosed with breast cancer. Genomic analysis for BRCA1 or BRCA2 mutations could be performed for 288 (90%) of these 320 women, on tissue prospectively procured from all trial participants.

A total of 19 (6.6%) of the 288 cases screened proved positive for BRCA mutations. Among the 8 women with BRCA1 mutations, 5 were in the tamoxifen group and 3 were in the placebo group (RR, 1.67; 95% CI, 0.32-10.70). Among the 11 women with BRCA2 mutations, 3 were in the tamoxifen group and 8 were in the placebo group (RR, 0.38; 95% CI, 0.06-1.56).

Among the 269 women without BRCA mutations, 87 received tamoxifen and 182 received placebo (RR, 0.48; 95% CI, 0.37-0.61). Among women with ER+ tumors, 132 received placebo and 41 received tamoxifen. Conversely, of those with ER- tumors, 32 received placebo while 36 received tamoxifen. ER status was not available for 28 of the wild-type tumors.

Although the results were not significant, the statistical trend suggested a protective benefit for tamoxifen use among women with BRCA2 mutations. Clinically, this conclusion is believable given the increased frequency of ER+ tumors in this group.[3] However, the sample size was simply too small to draw conclusions regarding women with BRCA1 mutations. Even using Fisher's exact test, the confidence interval was extremely wide for this group, and, furthermore, BRCA1 tumors are associated more frequently with ER- tumors suggesting that tamoxifen would be less relevant as a chemoprotectant.[3]

■ COMMENT BY ARDEN MORRIS, MD

Tamoxifen has now been shown to play a valuable role in prophylaxis of ER+ breast cancer, reducing risk by 49% among high-risk women, but has not shown a benefit for prevention of ER- malignancy.[1] These prophylactic benefits persist for younger women and women at especially high risk, even when weighed against the morbidity risks associated with tamoxifen.[4]

The subtext in this study by King et al centers on the especially high lifetime risk faced by women with BRCA1 and BRCA2 mutations, prompting some to recommend bilateral mastectomy as the only reliable prophylaxis for women who are likely to develop disease.[5] Although tumors associated with BRCA1 mutation tend to be ER-, possibly due to earlier de-differentiation, BRCA2 mutation-associated tumors are more frequently ER+, and therefore are more promising for tamoxifen prophylaxis. King et al have attempted to evaluate this less invasive method of prophylaxis by using data from what may be the last large randomization of tamoxifen vs. placebo in high-risk women (due to ethical implications of randomizing to placebo now).

Although their results did not reach statistical significance, King et al have conducted a cost-efficient, elegant analysis of the available data. The confidence interval for the limited BRCA1 data (95% CI, 0.32-10.70) is too large to draw any conclusions. The confidence interval for the BRCA2 data is substantially narrower (95% CI, 0.06-1.56) but certainly does not reach statistical significance. As King et al point out, the only discernable way to improve confidence intervals would have been to include twice as many subjects in the BCPT initially. Longer follow-up may provide more information; however, median follow-up in this study was a respectable 5.7 years. An alternative and prohibitively expensive study design might have been to enrich the BRCA1 or BRCA2 mutation-carrying cohort selection in the original data collection. On balance, the conclusion that women with BRCA2 mutations should undergo tamoxifen prophylaxis aligns with prior hypotheses and provides an alternative to major surgical intervention. ❖

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XRT to Prevent Local Breast Cancer Recurrence: A Little More is Better

ABSTRACT & COMMENTARY

Synopsis: The European Organization for Research and Treatment of Cancer (EORTC) has been examining the effects of an additional dose of 16 Gy beyond the typical 50 Gy to prevent local breast cancer recurrence in women with Stage I or II disease after breast conserving surgery and axillary node dissection. Although it is likely to take several more years to demonstrate a survival advantage for those who received the additional dose, analysis at 5 years demonstrates a clear advantage with regard to local recurrence. The boost dose was not associated with additional toxicity.

Source: Bartelink H, et al. *N Engl J Med*. 2001;345: 1378-1387.

There is well-established evidence that breast irradiation reduces the rate of local recurrence after breast conserving surgery for cancer. The standard dose of irradiation—50 Gy—has not been examined in a large, randomized trial. Bartelink and colleagues report the results of an EORTC trial in which patients with Stage I or II breast cancer after lumpectomy and axillary node dissection were treated with either conventional dose radiation or conventional dose with an additional boost of 16 Gy given in 2 Gy fractions.

During a median follow-up of 5.1 years, local recurrences were observed in 182 of the 2657 patients in the standard treatment group and 109 of the 2661 patients in the additional-radiation group. The 5-year actuarial rates of local recurrence were 7.3% (95% CI, 6.8-7.6) and 4.3% (95% CI, 3.8-4.7) ($P = 0.001$), yielding a hazard ratio for local recurrence of 0.59 (95% CI, 0.43-0.81) associated with an additional dose. Local recurrence was greatest in patients younger than 40 years of age, and in this group the beneficial effects of the additional dose of radiation were most significant. For this group, the rate of local recurrence was 19.5% with standard treatment and 10.2% with additional radiation (hazard ration, 0.46 [99% CI, 0.23-0.89], $P = 0.002$). There was no observed increased local toxicity produced by the added dose of radiation.

This study was powered to detect a difference in survival at 10 years, but, upon review of the data at 5 years, the difference in local recurrence was clearly significant. However, at 5 years, survival free of distant metastases and overall survival were similar in the 2 treatment groups, with rates of 87% and 91%, respectively. Thus, it is too early to conclude whether the additional radiation will result in improvement in these important outcomes.

■ COMMENT BY WILLIAM B. ERSHLER, MD

The B-06 trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated that after microscopically complete excision, irradiation to the whole breast with a dose of 50 Gy reduced the rate of local recurrence from 35% to 10%.[1] Since then, the 50 Gy dose has become the standard prescribed treatment. One purpose of the EORTC trial was to establish whether radiation beyond that dose would achieve even better results, and whether it could be accomplished without additional toxicity. Analysis at a median of 5 years post-therapy reveals positive findings. There is clearly less local recurrence with the added boost, and this with no added toxicity. There was approximately 40% less local recurrence in those receiving additional therapy.

Upon rigorous statistical analysis, Bartelink et al found that the groups at highest risk for local recurrence were, as expected, the ones most likely to benefit from the additional therapy. Included were young women (40 years and younger), in whom local recurrence rates dropped from nearly 20% to approximately 10%. Similarly, other risk factors, such as size of the primary, axillary node involvement and ER/PR status, were predictive of subgroups most likely to benefit from the boost.

As time passes, we will be learning more from this large and well-constructed EORTC trial. If it turns out that disease-free and overall survival are similarly enhanced by this additional therapy, it will not take long before standard radiation approaches after lumpectomy are adjusted upward. Certainly, local recurrences were not diminished to zero, and with the lack of additional short- or long-term toxicity with the added boost, investigators will be tempted to examine even higher doses or schedules.

Short of the survival data, however, is there enough here to change the standard 50 Gy approach? The only marginal improvements seen in those older than 50 years of age, and particularly in postmenopausal women with ER/PR positive tumors, when balanced with the added expense and inconvenience of 8 additional treatments would suggest that universal recommendations should not be applied. Furthermore, enrollment of patients older than the age of 70, which is approximately the median age of breast cancer in the United States, was not allowed in this trial. For these older patients, there will remain no data that would support additional therapy.

On the other hand, for young patients, with or without other negative prognostic factors, this study would support an additional boost of adjuvant XRT after lumpectomy. Even if later data indicate no improvement in overall survival, the reduction in local recurrence and the prevention of the need for salvage therapy would make such an approach worthwhile. ❖

Reference

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CME Questions

1. Regarding ovarian cancer patients with large volume ascites, which of the following did Kuhn et al demonstrate?

a. At least 3 cycles of neoadjuvant chemotherapy are needed to improve survival.
b. Patients with ascites should receive neoadjuvant intraperitoneal chemotherapy.
c. Both postoperative residual tumor (> 2 cm) and the volume of ascites appear to be prognostic factors.
d. Prior to neoadjuvant chemotherapy, ascites must be drained to prevent increased platinum toxicity.

2. BRCA1 and BRCA2 are:

a. both tumor suppressor genes.
b. both proto-oncogenes.
c. an oncogene and a tumor suppressor gene, respectively.
d. mismatched repair genes.

3. Tamoxifen provides chemical prophylaxis against developing breast cancer in:

a. women older than age 60.
b. women with lobular carcinoma in situ.
c. women with ductal carcinoma in situ.
d. a and b

4. In the SWOG/CALGB trial:

a. patients were ineligible for the study if they had B symptoms.
b. patients who were surgically staged were included.
c. those patients with uptake below the diaphragm on PET scan were randomized.
d. disease-free survival, but not overall survival, was shown to be better in the STLI arm.

5. Which of the following is *false* concerning the SWOG/CALGB Hodgkin's disease trial?

a. Patients could receive their radiotherapy on a cobalt unit.
b. Patients could receive their radiotherapy within 1 month of

completion of chemotherapy.

c. Patients could receive their mantle and paraaortic radiotherapy simultaneously.
d. All of the above

6. **The addition of 16 Gy beyond the typically administered 50 Gy for women with Stage I or II breast cancer after breast conserving therapy was associated with:**
   a. greater overall survival.
   b. greater disease-free survival.
   c. less local recurrence.
   d. All of the above

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