



Combined chemoradiation in high-risk endometrial cancer: benefit or not?

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Recently, the final results of the large scaled randomized intergroup trial named PORTEC-3 was released showing that adjuvant chemotherapy given concurrently during and after pelvic irradiation in women with high-risk endometrial carcinoma provided no significant 5-year failure-free (FFS) or overall survival (OS) benefit, compared with radiotherapy (RT) alone (1).

PORTEC-3 was multi-national trial conducted by six participating groups. The rationale of the trial was that significant portion of endometrial cancer patients have high-risk disease features, and these patients are at increased risk of distant metastases.

Thus far, several trials have showed promising results. A Radiation Therapy Oncology Group (RTOG) trial of concurrent chemoradiotherapy (CRT) showed promising results and a feasible toxicity profile (2). A phase III trial conducted by European Organization for Research and Treatment of Cancer (EORTC) suggested that sequential chemotherapy and RT was associated with improved progression-free survival (3). However, various chemotherapy schedules and sequences have been used in these trials, and no extensive quality of life analysis was done.

In PORTEC-3, radiation therapy and two cycles of three weekly concurrent cisplatin followed by four cycles of paclitaxel and carboplatin showed some promising results in its effectiveness, and quality of life analyses showed no difference between groups.

The 5-year FFS rate in 330 women who received both chemotherapy and RT was 76%, *vs.* 69% in 330 women who received only RT [hazard ratios (HR), 0.77]. The

respective 5-year overall survival rates were 82%, *vs.* 77% (HR, 0.79). Although the differences did not reach statistical significance, there was a trend for better FFS beginning after 1 year and a small suggestion for an OS benefit after 3 years in groups treated with chemotherapy and RT.

Five-year FFS and overall survival of study participants with stage III endometrial cancer were significantly lower than in those with stage I–II disease (64% *vs.* 79% and 74% *vs.* 83%, respectively), but those with stage III disease experienced the greatest benefit with adjuvant chemotherapy showing that 5-year FFS was 69% for those with stage III treated with RT plus chemotherapy, *vs.* 58% for those treated with RT alone.

In toxicity profile, the patients who received CRT experienced greater toxicity including bone marrow suppression, diarrhea, fatigue and peripheral neuropathy. However, there was significant recovery in the majority of severe side effects without significant differences at 1 and 2 years after randomization except for peripheral neuropathy.

Another important randomized trial named GOG-258 which randomized patients to the same CCRT regimen as that used in PORTEC-3 or to chemotherapy alone recently released unpublished interim data showing that the CRT did not improve recurrence free survival compared to chemotherapy alone (HR 0.9, 95% CI: 0.74–1.1). However, it is important to consider that GOG 258 still showed a significant effect of RT on decreasing regional and local recurrences. Vaginal vault recurrence incidence at 5 years was 3% in the CRT arm *vs.* 7% in the chemotherapy arm (HR 0.36, 95% CI: 0.16–0.82). CRT

also reduced pelvic and para-aortic recurrence incidence by 10% compared with the chemotherapy arm (19%; HR 0.43, 95% CI: 0.28–0.66) (4).

Based on these findings, additional chemotherapy is not recommended for women with high risk stage I–II because these group showed excellent survival with post-operative RT alone. However, considering the higher risk of recurrence in patients with stage III disease, the CRT should be considered, and the potential benefits and harms should be individually discussed. In addition, we need to consider to include CRT when we design future trials and pursue novel strategies given the results from GOG 258 and PORTEC-3.

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