Frequency and Effect of Adjuvant Radiation Therapy Among Women With Stage I Endometrial Adenocarcinoma

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Background

- Endometrial cancer is the most common gynecological malignancy in the U.S.
- The majority of cases are Stage I, and overall survival is 80-90% at 5 years.
- Standard treatment for Stage I endometrial cancer is total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH-BSO) +/- lymph node sampling.
- Adjuvant radiotherapy (RT) is controversial. Major questions still exist:
    - which Stage I patients should be treated with adjuvant RT?
    - which patients should be treated with pelvic RT, vaginal brachytherapy (VB), or both?
- Phase 3 trials have shown that the addition of pelvic RT improves locoregional control, but not overall survival

Methods

- Design: Retrospective analysis of patients from the Surveillance, Epidemiology, and End Results (SEER) database
- Patients: Stage I endometrial cancer treated with TAH-BSO diagnosed between 1988 and 2001
    - 21,249 women with complete data sets, including pathologic information (grade from 1 to 3; depth of invasion) and treatment (documented hysterectomy; use of RT).
    - Because the SEER database lacks detailed information regarding relapse, the main endpoints were overall survival and relative survival.
    - Cause of death was determined from death certificates.
    - Median follow-up was 46 months (range, 0.1 to 167 months).

Results

- 19.2% received postoperative RT, (63% external beam RT, 18% vaginal brachytherapy, 26% had both); higher grade and stage were associated with increased use of RT
    - 57% of Stage IC patients received postoperative RT
- 43% had surgical nodal sampling
- The addition of RT improved overall survival and relative survival in Stage IC grade 1 (HR 0.44, 95% CI 0.21-0.63) and Stage IC grade 3/4 patients (HR 0.72, 95% CI 0.57-0.92), but interestingly, not in any other stage/grade subgroup, even 1C grade 2 patients

- RT was associated with a ~10% improvement in overall survival at 5 years in IC grade 1 and IC grade 3/4 patients, with the greatest benefit in older patients:
    - IC1:
        - below age 56: 98% vs. 88%
        - 56-75 yrs: 94% vs. 85%
        - over age 75: 84% vs. 67%
    - IC3/4
        - below age 56: 86% vs. 77%
        - 56-75 yrs: 66% vs. 56%
        - over age 75: 53% vs. 39%
- The benefit of RT was also seen in the subset of Stage IC1 and IC3/4 patients who underwent surgical lymph node sampling
- White race (HR, 0.8; 95% CI, 0.62-1.02) and surgical lymph node sampling (HR 0.89; 95% CI 0.80-1.0) were associated with trends toward improved relative survival that were not quite significant.

Discussion

- This is the largest reported retrospective, population-based study examining the prognostic factors and the effect of treatment-related parameters on survival in patients with Stage I endometrial cancer.
- RT was associated with improved overall survival and relative survival for patients with stage IC1 and IC3/4 endometrial cancer.
- Survival benefits have not been observed in randomized trials, which may be attributable to inadequate power and limited follow-up.
- Limitations of this study include its retrospective design, limited detailed information on important prognostic factors (lymphovascular invasion, precise depth of invasion, lower uterine segment involvement, specifics of RT), and inability to assess event free survival due to the inherent limitations of the SEER database.
- The surprising observation that Stage I, grade 2 patients did not seem to benefit from RT was attributed to relatively small sample sizes in each subgroup and inherent difficulties in assigning grade.

Comments

- The observation that RT is associated with improved survival in most Stage IC endometrial cancer patients is a significant finding, because underpowered previous phase III randomized trials have only demonstrated locoregional control benefits from adjuvant RT.
- Although a major strength of this study is the large sample size drawn from the SEER database, an inherent weakness is the fact that RT treatment was not randomized. However, the authors correctly point out that the addition of postoperative RT usually occurs in patients with worse prognostic signs, and thus they would be expected to fare worse. Any benefit of RT would likely by masked by selection of poorer prognosis patients. This may help explain the puzzling lack of benefit in Stage IC2 patients
- From a "patterns of care" perspective, it is interesting that only 57% of Stage IC patients received RT according to the SEER database. Perhaps more of these patients should be receiving adjuvant RT.
- The important question of which patients should receive pelvic RT, vaginal brachytherapy, or both was not addressed by this study.
- This study emphasizes the impact of local control on overall survival in endometrial cancer, a phenomenon that has also been demonstrated in other disease sites (e.g. early stage breast cancer).