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Revisiting Milan cervical cancer study: Do the original findings hold in the era of chemotherapy?

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HIGHLIGHTS

- Radiation and Hysterectomy are equivalent in treating early stage cervical cancer
- Concurrent chemotherapy is of benefit in the definitive and adjuvant setting
- The benefit of chemotherapy has never been directly compared for each modality
- Definitive and adjuvant chemoradiation provide similar overall survival

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ABSTRACT

Background. The primary treatment of early stage cervical carcinoma (IB-IIA) is either surgery or radiation therapy based on the pivotal Milan randomized study published twenty years ago. In the presence of high-risk features, the gold standard treatment is concurrent chemotherapy and radiation therapy (CRT) whether it is the in the postoperative or the definitive setting. Using the National Cancer Data Base (NCDB), the goal of our study is to compare the outcomes of surgery and radiation therapy in the chemotherapy era.

Methods. Between 2004 and 2013, 5478 patients diagnosed with early stage cervical cancer were divided into 2 groups based on their primary treatment: non-surgical ($n = 1980$) and surgical groups ($n = 3498$). The distribution of patient/tumor characteristics and treatment variables with their relation to overall survival and proportional regression models were assessed to investigate the superiority of one approach over the other. Propensity score analysis adjusted for imbalance of covariates to create a well-matched-patient cohort.

Findings. At 46 months median follow-up, the 5-year overall survival was similar between both groups (73·8% vs. 75.7%; $p = 0.619$) after applying propensity score analysis. On multivariate analysis, high Charlson comorbidity score, stage IIA disease, larger tumor size, positive lymph nodes and high-grade disease were significant predictors of poor outcome while older age and treatment approach were not.

Interpretation. Our analysis suggests that surgery (followed by adjuvant RT or CRT) and definitive radiotherapy (with or without chemotherapy) result in equivalent survival. Prospective studies are warranted to establish this paradigm in the chemotherapy era.

1. Introduction

Although screening strategies have decreased cervical cancer (CC) incidence and mortality [1], it remains a major health problem that affects 12,200 patients in the United States [2] and >500,000 patients worldwide on annual basis [3].

For patients presenting with early stage (IB-IIA) CC, definitive radiotherapy (RT)/concurrent chemoradiotherapy (CCRT), neoadjuvant

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chemotherapy with hysterectomy, or radical hysterectomy (with or without adjuvant RT or CCRT) are all considered standard treatment options by the current management guidelines with comparable tumor control, survival and toxicity [4]. This treatment paradigm is largely influenced by the pivotal Milan University study published by Landoni et al. almost two decades ago [5]. Powered to detect survival advantage, this randomized trial did not reveal a statistical difference in either overall survival (OS) or disease-free survival (DFS) in 343 patients with early-stage CC treated with radical hysterectomy versus radiation alone. However, two thirds of the patients randomized to the surgical arm received adjuvant RT leading to a significant increase in toxicity in this subgroup of patients. This study demonstrated that definitive RT is not only equivalent to radical surgery but it may be the preferred approach for tumors larger than 4 cm that are more likely to display adverse pathologic features: positive lymph nodes (26%), positive surgical margins (11%) and higher pathologic stage (24%). These features would otherwise require two treatment modalities with higher expected toxicity.

After the publication of this study, multiple randomized trials and meta-analyses documented a consistent survival advantage with the addition of chemotherapy to RT in both the adjuvant and the definitive setting [6–10]. In Peters et al. study, patients with the aforementioned adverse features were randomized to adjuvant CCRT versus RT alone. Adjuvant CCRT resulted in an OS benefit at four years (81% vs. 71%, $p = 0.007$) [7]. Similarly, definitive CCRT as compared to definitive RT alone has shown to improve overall survival [6,8,9]. Consequently, definitive CCRT adjuvant CCRT became the gold standard in the management of stage IB2-IIA CC disease and is indicated in early stage CC with adverse risk factors after radical hysterectomy, respectively.

Since the outcomes of definitive CCRT and those of surgery followed by adjuvant CCRT were never compared in a prospective randomized fashion, we used the National Cancer Database (NCDB) to re-evaluate the validity of Landoni's study in the era of chemotherapy. We compared the surgical with the non-surgical approach questioning if the addition of chemotherapy would improve the survival in one approach over the other and we hypothesized that, akin to the original Milan study, both paradigms will lead to similar overall survival even with chemotherapy integration.

2. Methods and materials

The American College of Surgeons and the American Cancer Society sponsor the NCDB that abstracts hospital registry data from >1500 accredited facilities collecting nearly 70% of newly diagnosed cancer cases nationwide [11]. In 2016, the institute review board exemption was granted and the study queried the database for women diagnosed with cervical cancer from 2004 through 2013 yielding 98,347 patients.

Emulating Milan study eligibility criteria, the NCDB coding key [12] was employed to select 30 to 70 year old patients who were diagnosed with non-metastatic International Federation of Gynecology and Obstetrics (FIGO) [13] stage IB-IIA invasive cervical cancer (or American Joint Committee on Cancer (AJCC) [14] T-stage whenever FIGO stage was missing).

Patients with missing treatment information, those receiving adjuvant or definitive CCRT with non-coinciding chemotherapy and radiotherapy start date and/or those who did not receive radical treatment as their primary treatment approach were excluded yielding 5478 patients constituting the entire study cohort (eFig. 1).

The analysis included demographics, socioeconomic and clinical covariates such as age, race, Charlson-Deyo comorbidity score, insurance status, median income of ZIP code, education level, treatment facility type, distance to hospital, tumor size, grade, lymph node status, histology, margin status and clinical stage.

Fisher Exact Chi-square test [15] was employed to assess the distribution of these prognostic variables per type of primary treatment delivered. OS was estimated using the Kaplan-Meier method and log-rank test [16]. The association between survival outcomes and treatment strategy was analyzed with multivariable proportional Cox proportional hazards models [17]. As the hazards model may not address the profound difference of covariables between the treatment subgroups, propensity-score matching was used to compare surgically treated patients to those treated with definitive RT. The model was limited to those independent variables with impact on survival hazard rates such as age, FIGO stage, comorbidity score, histology, lymph nodes, tumor size, grade (treatment modality was the dependent variable). The cohort was matched one to one using nearest neighbor technique with a caliber distance of 0.025 thus limiting standardized difference to 0.15 or less [18].

A study would be able to reject the null hypothesis where a treatment option results in significant mortality reduction with 80–85% power if it accrues 1350–1650 patients in four years assuming two years follow up period and assuming eight and a half to ten years' median survival for stage IB-IIA. The Type I error probability associated with this test of the null hypothesis is 0.05 if the hazard ratio is 1.35. The total number of events will be 350 in this non-inferiority, non-superiority, two-treatment parallel-design study [19]. All analyses in this study were 2-sided with $P \leq 0.05$ conducted in R statistical environment (R Development core team (2015), version 3.2.2) [20].

3. Results

Among the 5478 patients with early stage cervical cancer treated definitively between 2004 and 2013, the median age was 45 years, 87.6% did not have comorbidity and 89.6% were insured.

In this cohort, surgery was the favored approach which was used in 64% of the patients. The baseline patient's characteristics are summarized in Table 1. The non-surgical approach was commonly observed in academic affiliated centers or centers located within 25 miles from patients' residence. Similarly, it was favored in patients with higher stage, advanced age, larger size, higher grade tumors with positive lymph nodes and with squamous histology. Black patients with lower income and lower education were more likely to receive non-surgical management. However, year of diagnosis, comorbidity score or rural residence were evenly balanced in the surgical and non-surgical groups.

At a median follow up of 46 months (Interquartile range (IQR): 25–75 months), the 5-year overall survival in the unadjusted groups was higher in the surgery group (Fig. 1); 87% (95% confidence interval (CI): 85.6–88.6%) vs. 61% (CI: 67.1–72.4%) in the non-surgical group due to profound imbalance of early stage, small-sized disease in this group. Similar conclusion was held on displaying survival by stage (eFig. 2). Multivariable proportional hazards model demonstrated that age older than 60, higher comorbidity score, and black race were associated with worse outcomes (eTable2). Moreover, tumors larger than 4 cm, higher grade disease and positive pelvic lymph nodes, but not histology, were associated with higher mortality. Histology however was not correlated to increased mortality. Nevertheless, the multivariate analysis of survival (MVA)- adjusting for cofounders- did not favor one paradigm over the other; the hazards ratio (HR) for the cohorts undergoing surgery was 0.93 (CI: 0.76–1.1; $p = 0.47$) when compared to those who were managed with radical radiotherapy (eTable 2).

The covariates potentially impacting the choice of treatment or survival outcomes were included in the propensity score matching; a cohort of 1644 patients was generated displaying well-balanced distribution of categorical variables (between the surgical and non-surgical cohorts) with standardized difference below 15%. Besides minor differences in the age and comorbidity score percentages in the two cohorts (favoring healthier younger patients' characteristics in the surgery group), the remaining covariates were evenly distributed in both groups (eTable 2). A stricter matching would have resulted in a well-balanced distribution of all the covariates on the expenses of acquiring a small population size not powered to reject the null hypothesis (Table 2).

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