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Original article

Refusal of postoperative radiotherapy and its association with survival in head and neck cancer

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ABSTRACT

Background and purpose: Administering postoperative radiotherapy (PORT) is associated with improved survival and slower disease progression in select head and neck cancer patients. Predictive factors for PORT refusal have not been described in this population.
Materials and methods: Retrospective analysis of 6127 head and neck cancer patients who received or refused PORT in the National Cancer Database (2003–2006) was performed. Statistical analysis included Chi-square, multivariable logistic regression, Kaplan–Meier, and Cox proportional hazards analysis.
Results: In total, 247 patients (4.0%) refused PORT. Three-year overall survival was 62.8% versus 53.4% for those who received and refused PORT, respectively. PORT refusers were more likely to have negative nodes than those who underwent PORT (37.4% versus 20.1%, $p < .001$). In multivariate analysis, predictive factors for refusing PORT included living far from the treatment facility (OR 1.92), having negative nodes (OR 2.14), and Charlson score of $\geqslant 2$ (OR 2.14) (all $p \leqslant .001$). PORT refusal was associated with increased mortality (hazard ratio 1.20, $p = .044$).
Conclusions: A significant proportion of head and neck cancer patients refused PORT; this was associated with compromised overall survival. Predictive factors for PORT refusal included socioeconomic, demographic, and pathologic variables. Elucidating root causes of refusal may lead to interventions that improve long-term outcomes.
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For select head and neck cancers, postoperative radiotherapy (PORT) is an available treatment option that may or may not be combined with chemotherapy in the adjuvant setting [1,2]. The use of PORT has increased over several decades [3], and has been shown to offer significant benefits in survival and disease control [4,5], including in patients with high-risk pathologic features such as positive margins or extracapsular extension (ECE) [6].

Radiotherapy in the head and neck has several well-characterized complications including dysphagia, mucositis [7], osteoradionecrosis [8], and xerostomia [9]. These toxicities must be weighed against potential gains in the context of patient factors and goals of care. Curative therapies may not be administered due to comorbid conditions, noncompliance [10], or refusal by patients or guardians. Risk factors and reasons for refusal of oncologic therapy are varied [11–13], and have not been well-characterized in head and neck cancer patients. As refusal of recommended radiotherapy has been associated with compromised survival [12], this topic warrants further investigation.

We sought to determine the scope of PORT refusal, identify predictive factors for refusing PORT, and to analyze the impact of refusal on overall survival in the head and neck cancer population. We hypothesized that socio-demographic and disease-related factors would impact patients' decisions to refuse PORT.

Methods

Datasource

We performed a retrospective cohort analysis of 6127 patients receiving or refusing recommended PORT in the National Cancer Database (NCDB) between years 2003 and 2006. The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, and contains

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data from over 1500 CoC-approved hospitals [14]. Coding guidelines are dictated by the Facility Oncology Registry Data Standards (FORDS) manual [15].

Selection criteria

We included patients with tumor primaries located in the oral cavity (C00.0–00.6, 00.8–.9, 02.0–02.3, 02.8–.9, 03.0–.1, 03.9, 04.0–.1, 04.8–.9, 05.0, 05.8–06.2, 06.8–.9), oropharynx (C01.9, 02.4, 05.1–.2, 09.0–.1, 09.8–.9, 10.0–10.4, 10.8–.9), hypopharynx (C12.9, 13.0–.2, 13.8–.9), glottic- (C32.0, 32.2–.3, 32.8–.9), and supraglottic larynx (C32.1), as determined by International Classification of Disease for Oncology, 3rd edition (ICD-O-3) site topography codes [16]. We excluded patients with nasopharyngeal primaries, as treatment does not typically include surgical intervention. All patients in our cohort underwent resection of the primary lesion; cases coded as a local destruction not producing a pathologic specimen were not included. We also excluded patients with nodal metastases and advanced tumors who did not undergo neck dissection as per the 2015 NCCN Guidelines® [17]. Patients who received preoperative radiotherapy, had prior malignancies, received palliative therapy, or had classifications T0, TX, Tis, NX, or overall clinical Stages 0 and IVC were also excluded. Patients not receiving PORT for other reasons, including not being part of the planned course of treatment, patient comorbidity, or death prior to start of therapy, were not included in our analysis. We then queried patients in the database with complete information for the following variables: patient gender, age, race, Hispanic origin, insurance status, income, education, proximity to metropolitan area, distance from the treatment facility, facility type, Charlson–Deyo comorbidity index (recorded after 2003), tumor primary site, clinical TNM classifications, overall clinical stage, and treatment-related variables such as undergoing surgery of the primary site, reason for no radiotherapy, surgical margin status, and summary of systemic therapy.

Variable definitions

Variable definitions are consistent with the NCDB Data Dictionary [18], with some exceptions. Patients of Hispanic origin were labeled as Hispanic, and this information was incorporated into the race variable. Proximity to a metropolitan area is based on codes set forth by the United States Department of Agriculture [19], and was characterized as either in, adjacent to, or nonadjacent to a metropolitan area, regardless of population size. Distance from the treatment facility that reported the case was listed as either $\geqslant$29.8 miles (top quartile for the cohort) or <29.8 miles (all other). Patients may have received all or a portion of the first course of treatment at the reporting facility. Facility type reflects the classification as designated by the CoC accreditation program [18], and was stratified into Academic/Research Cancer Programs (ARPs) and non-ARPs [20]. Facility volume was divided into high-volume ($\geqslant$90th percentile, or $\geqslant$14 cases) and low-volume as it pertained to head and neck cancer during the study period. Clinical stage and TNM classifications are based on the American Joint Committee on Cancer (AJCC) staging system, 6th edition [21]. AJCC overall clinical stage was characterized as I, II, III, IV, or as early- (Stages I and II) and late-stage (Stages III and IV) disease. Those patients listed as receiving regional lymph node surgery were coded as having received a neck dissection [20], although extent of neck dissection is not recorded. Surgical margin status was characterized as either being negative (grossly and microscopically) or positive (microscopic, macroscopic, or unspecified). ECE was determined pathologically or clinically, with clinically-determined ECE defined by the following: "imaging studies showing amorphous spiculated margins of involved nodes or involvement of intermodal fat resulting in loss of normal oval-to-round nodal shape strongly suggesting extracapsular tumor spread" [22]. Patients were then listed as either having received or refused recommended PORT. Refusal of therapy may have been stated by the patient, a family member, or guardian, and was noted specifically in the chart [18]. Data for this variable, which have been collected since at least 1998, were present for all patients in our cohort.

Statistical analysis

Statistical analyses were performed using SPSS 22.0.0 for Mac (Chicago, IL). Demographic and disease-related data were presented using standard descriptive statistics. Pearson Chi-square and Kaplan–Meier log-rank tests were used for univariate analysis, with $p \leqslant .10$ used as a cut-off for inclusion into multivariable logistic regression models. Analysis of overall survival was performed using Cox proportional hazards regression. All tests were two-sided, and the final threshold for significance was $p \leqslant .05$.

The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data. This study was granted exemption by our institutional review board.

Results

A total of 6127 patients were available for analysis, 4.0% of which refused PORT. Median follow-up time was 57.5 months (range 0.76–117.65 months). In those who received PORT, median radiation dose was 60.0 Gy over a median 33.0 treatments. External beam radiotherapy was administered in 97.9% of patients receiving radiotherapy. Three-year overall survival was 62.8% versus 53.4% for those who received and refused PORT, respectively. Patients who refused PORT were more likely female, aged $\geqslant$65 years, had non-private insurance, had an annual income of < $30,000/year, and had a Charlson score >0 on univariate analysis (Table 1). Refusers of PORT were also more likely to have $N > 1$ necks, Stages II and III disease, and primary tumors of the supraglottic larynx and oral cavity.

Patients who refused PORT were more likely than those who received PORT to have all examined nodes negative (37.4% versus 20.1%, respectively, $p < .001$). They were also less likely to have 1–10 positive nodes (33.3% versus 45.9%, $p < .001$). While data regarding ECE were largely missing, we found 12.2% in total had pathologically-determined ECE, 1.1% had ECE clinically, and 21.2% had no ECE. Patients who received PORT did not have significantly higher rates of ECE than their counterparts who refused ($p = .392$).

Median estimated survival was significantly lower for PORT refusers (56.1 months, 95% CI 37.2–75.0 months) compared to those who received PORT (92.0 months, 95% CI 87.0–97.1 months) ($p < .001$) (Fig. 1a). When stratified by early and late stage disease, PORT refusal was associated with worse overall survival in late ($p < .001$) (Fig. 1b), but not early stage disease ($p = .060$).

In multivariate analysis, factors associated with PORT refusal included insurance status, living far from the treatment facility, Charlson score >0, and having all examined nodes negative (Table 2). In multivariable analysis, PORT refusal was associated with compromised overall survival (hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.01–1.44, $p = .044$) when all patients were combined and when the model was adjusted for socioeconomic, demographic, and disease-related factors (Fig. 2). Similarly, PORT

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