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EDITORIAL

Hypopharyngeal cancer: looking back, moving forward

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Population-based datasets can provide observational insights into cancer incidence, patterns of care, and trends in survival outcomes. They can be particularly valuable in rare cancers for which there can be a paucity of prospective evidence. In this issue of *Current Oncology*, Hall describes treatment and survival trends in 1333 patients with squamous cell carcinoma of the hypopharynx (HPC) treated between 1990 and 2010 in Ontario, based on data from the Ontario Cancer Registry, with linkages to three other administrative datasets[1].

As a rare malignancy, HPC accounts for fewer than 5% of head-and-neck cancers and portends a poor prognosis, driven by patient, anatomic, and disease factors[2]. Patients with HPC have high rates of tobacco- and alcohol-related comorbidities and second cancers and frequently come from lower socioeconomic backgrounds[3,4]. Late presentation is typical, with approximately 70%–90% of patients having stage III or IV disease at the time of presentation, and is at least in part attributable to the anatomy and location of the hypopharynx[3–6]. The underlying disease-related biologic factors are less well understood, but compared with other head-and-neck sites, HPCs have high rates of multicentricity, submucosal spread, and regional and distant metastasis[7]. In retrospective series, approximately 60% of patients treated with curative intent experience disease relapse or residual disease, and up to 50% of recurrences involve distant failure[3,4].

Evidence-based practice in HPC is challenged by the low incidence of the disease and is largely based on extrapolations from clinical trials in laryngeal squamous cell carcinoma (SCC) and subgroup analyses of multi-site head-and-neck SCC trials. Despite the substantial heterogeneity in study methods and characteristics, randomized trials comparing concurrent chemoradiation with radiation alone or radiation after induction chemotherapy in locally advanced head-and-neck SCC have generally demonstrated improved local outcomes, including larynx preservation, with inconsistent conclusions on survival benefit[8–12]. The Meta-Analysis of Chemotherapy in Head and Neck Cancer collaborative group, in a subgroup analysis of 2767 HPC patients, found a 5-year absolute survival improvement of 4% associated with concomitant chemotherapy (hazard ratio: 0.85; 95% confidence interval: 0.75 to 0.96) compared with radiotherapy alone[13]. Thus, based on those data and equipoise on optimal treatment, a shift from open surgery toward multimodality approaches for organ preservation has occurred in HPC despite the greater risk of acute and potentially chronic toxicities from concomitant chemotherapy[14,15].

Consistent with other population-based series, Hall observed an increase in the prevalence of concurrent chemoradiation in the post-2000 era and a decrease in the use of primary surgery or radiation alone, with no statistically significant difference in overall survival between the treatment groups[1,2]. Hall's main finding is the lack of a survival increment over the 20-year study period, leading to the conclusion that the addition of concomitant chemotherapy to definitive radiotherapy did not yield survival gains[1].

However, several limitations in the study confound the ability to draw parallels between the observed survival trend and treatment effect. Firstly, the main determinant of outcome and treatment modality—that is, staging information—is absent. Secondly, patients are segregated into broad treatment groups with little detail about the regimen or schedule. The 30% of patients who received palliative or no treatment, or who had an incomplete treatment history, were assigned to the "no treatment" group. In fact, only 12% of patients received concurrent chemoradiation, a proportion that is unlikely to meaningfully affect the survival of the overall cohort. Lastly, the lack of information on cause of death is confounding given the frequency of significant comorbidities (more than 30% of patients in the cohort had at least 2 comorbidities as measured by the Elixhauser index) and second cancers in HPC[1]. In an earlier report based on the same database, 24% of deaths at 3 years were as a result of non-HPC causes[4].

Caveats notwithstanding, Hall's study draws attention to the compelling observation that no or minimal improvement in survival has occurred in HPC since the 1990s. Over a similar period, reports from the U.S. Surveillance, Epidemiology, and End Results database and the Netherlands Cancer Registry both showed nonsignificant marginal improvements (4%–6%) in 5-year relative survival (approximately 33% in both studies) in HPC[16,17]. In laryngeal SCC, no survival improvement or slightly declining survival was seen[2,16,17]. Those observations contrast with the marked 12%–22% survival improvement found in oropharyngeal SCC, likely driven by the epidemiologic increase in HPV (human papillomavirus) as the cause of the disease, a molecularly distinct and clinically favourable entity compared with HPV-negative head-and-neck SCC[16–20].

Progress in the management of head-and-neck SCC since the 1990s, such as the advent of intensity-modulated radiotherapy and concurrent chemoradiation, has led to

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improved local and functional outcomes. Disappointingly, long-term survival in HPC has not shifted beyond its historical 30%[2,3]. Thus, innovative therapies are urgently needed to improve outcomes in this treatment-resistant disease. Radiotherapy and surgery remain the primary modalities for cure, and any technical advances should bear in mind the parallel goals of improving survival and preserving function and quality of life. Chemotherapy can be complementary in selected curative settings and valuable for symptom palliation in advanced disease. Individualized treatment selection by an experienced multidisciplinary team is essential. Additionally, growing knowledge of the genomics of HPV-negative SCC and of immunotherapeutics have informed novel treatments, including rational intensification and combination strategies, which are under active investigation in the relapsed or metastatic and radical settings, offering unprecedented opportunities to transform this disease. Lastly, personalized supportive care and ongoing public health efforts targeting tobacco control and health care disparities remain vital to serve and advocate for this often under-resourced patient population.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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