

# Determining the survival benefit of adjuvant radiotherapy in patients with node-positive head and neck cancer

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Postoperative radiotherapy with or without chemotherapy remains part of the standard treatment regimen to improve locoregional control for patients with head and neck cancer who have adverse pathologic factors after surgery. Whether an overall survival benefit can be expected remains unclear.

## Summary

Whether postoperative radiotherapy improves survival compared with surgery alone in head and neck cancer remains unclear. This Practice Point discusses the findings of a study by **Kao et al.**, who used the SEER database to look for evidence of improved overall survival in patients with node-positive head and neck cancer (**Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer.** *Int J Radiat Oncol Biol Phys* 71:362–370). The analysis included 5,297 patients who were treated with first-line surgery, of whom 4,307 (81%) received adjuvant radiotherapy. Adjuvant radiotherapy, age, primary tumour site, tumour and nodal stage were significant predictors of overall survival. While the results show an association between use of adjuvant radiotherapy and improved overall survival in a selected group of patients, several aspects of the study limit its interpretation. Whether there is a causal relationship between postoperative radiotherapy and the observed overall survival benefit remains undetermined.



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**H**istorically, curative treatment of head and neck cancer consisted of radical resection. Radiotherapy was reserved for the treatment of tumour recurrence or palliation of disease where surgery was not indicated. In the mid-1950s, the basic principles of radiation biology were discovered, such as the steep dose–response curve whereby small changes in radiation dose could have large effects on tumour cells, as well as on the extent of damage to normal tissues. The need for molecular oxygen to be present for radiation to affect cells, and the relationships between tumour volume, hypoxia and disease control were also recognised at that time.<sup>1</sup> Over the next

20 years, techniques were developed to optimise radiotherapy dose distribution on the basis of tumour concentration, areas at risk for subclinical disease, and improvement of locoregional control.

Unlike most other solid tumours, the majority of head and neck squamous cell carcinomas (HNSCC) recur at the primary site or in the neck lymph nodes. The primary goal of all head and neck cancer therapies has, therefore, been to reduce locoregional failure rates as an essential step towards improved survival. In the 1970s, surgeons and radiation therapists reported data analyses of large case series from major centres in the US in order to define the pathologic features associated with an

increased risk of recurrence after surgery. For example, in a series of 1,775 patients with HNSCC of various primary sites, the incidence of primary site recurrence was 31.7% if surgical margins were negative and 71% if they were positive. This high recurrence rate did not differ whether carcinoma *in situ* or invasive carcinoma was present at the margin or within 5 mm of the margin.<sup>2</sup> Other pathologic features that indicated a need for postoperative radiotherapy were the presence of perineural or lymphovascular invasion, cartilage or bone invasion and high-grade histology. Recurrence in the neck was associated with the presence of multiple positive nodes and extracapsular extension (tumour spread through the capsule of the node) as well as high-grade histology.<sup>3-4</sup> Over several decades postoperative radiotherapy for patients with 'high-risk' disease evolved into standard clinical practice in the absence of randomised, controlled trials. Improved locoregional control seemed apparent from non-comparative trials and case series but an absolute survival benefit was less certain.

Kao and colleagues<sup>5</sup> used the Surveillance, Epidemiology, and End Results (SEER) database to look for evidence of improved overall survival and cancer-specific survival in various subgroups of patients with node-positive head and neck cancer. A total of 5,297 patients with node-positive, invasive HNSCC (excluding carcinoma of the nasopharynx, salivary gland and unknown primary sites) who were treated with first-line surgery were included, 4,307 (81%) of whom received adjuvant radiotherapy. Demographic data (age, sex, ethnicity, year of diagnosis), nodal stage, nodal surgery and primary tumour site, size, stage and

tumour grade were evaluated in univariate analysis and as continuous variables in multivariate analysis. The primary and secondary endpoints were overall survival and cancer-specific survival, respectively. Patients were diagnosed between 1988 and 2001 and surviving patients had been followed up for a median of 4.4 years.

On univariate analysis the authors found adjuvant radiotherapy significantly improved three-year overall survival (58.3% vs 43.6%,  $P < 0.001$ ) compared with surgery alone (95% CI 42.8–49.1%,  $P < 0.001$ ). On multivariate analysis, adjuvant radiotherapy, age, primary site, tumour and nodal stage were significant predictors of overall survival. Multivariate analyses of patients with N1–2a and N2b–3 disease showed significantly improved survival for all nodal subgroups, with the relative risk reduction being greatest for the N2b–3 cohort (HR 0.62, 95% CI 0.51–0.75,  $P < 0.001$ ).

While these results show an association between the use of adjuvant radiotherapy and improved overall survival in patients with positive neck nodes, several aspects of the analysis are worth commenting on. The 5,297 patients analysed represent a subgroup of the 8,507 individuals with positive nodes (62%). Although all patients had undergone first-line surgery, only an unspecified proportion of node-positive patients had undergone surgery in the neck. The neck staging system used in the paper, therefore, has to be considered to have a clinical basis and this approach contrasts with the current practice of prescribing radiotherapy according to the pathological stage. Surprisingly, the most prevalent primary site was the oropharynx, which differs from the current experience of most institutions (which use radiotherapy

alone or in combination with chemotherapy as the first-line treatment for this HNSCC subtype) and conflicts with the reported prevalence of HNSCC subtypes in the same time period in the SEER database (wherein the oropharynx follows the oral cavity and larynx).<sup>6</sup> These findings, along with the fact that the SEER database lacks information on the type and extent of surgery and reasons to prescribe or withhold adjuvant radiotherapy, hamper the interpretation of the study and its applicability. Moreover, the SEER database lacks data on patient performance status, on several important pathologic features (e.g. margin status, extracapsular extension, perineural or lymphovascular invasion), on the use of adjuvant chemotherapy and on the details of radiotherapy – factors that could all potentially affect outcome.

In conclusion, controversy remains over whether radiotherapy improves overall survival after first-line surgery in patients with HNSCC and positive neck nodes. While the paper from Kao et al. shows an association (but not a causal relationship) between radiotherapy and survival, the current adjuvant treatment paradigm has moved beyond adjuvant radiotherapy alone to include a recommendation for concomitant chemotherapy and radiotherapy in selected patients with high-risk disease.<sup>7</sup> Adjuvant chemotherapy and radiotherapy after surgery has a demonstrated advantage in locoregional control compared with radiotherapy alone in selected patients after surgery. The question remains as to whether the magnitude of the improvement is sufficiently large to affect survival.

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