### Advances in Radiation Oncology: What to Consider



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### **KEYWORDS**

- Radiation Chemoradiation Head and neck cancer Proton therapy HPV
- TORS IMRT IMPT

### **KEY POINTS**

- Further refinement to intensity-modulated radiotherapy (IMRT) planning continues to improve long-term swallowing and xerostomia outcomes.
- Deintensified therapy with dose de-escalated radiotherapy and transoral robotic surgery (TORS) are both potentially practice changing in head and neck cancer treatment.
- The optimal adjuvant therapies after TORS are still being defined.
- Modern proton therapy seems to reduce short-term and long-term toxicity for head and neck cancer treatment compared with contemporary IMRT, and it may further improve as intensity-modulated proton therapy (IMPT) continues to develop.

#### INTRODUCTION

Changing patient demographics and advances in radiation therapy techniques have significantly altered the head and neck cancer landscape. This review discusses active areas of investigation and technological improvements that are changing the practice of radiation oncology. IMRT continues to be refined to maximize quality of life (QOL) while maintaining excellent locoregional control outcomes. For example, additional exploration into radiation dose constraints to normal structures for treatment planning has yielded further QOL improvements. Deintensified regimens in the human papilloma virus (HPV)-related setting have emerged using different strategies, including reduced radiation dose regimens and the incorporation of TORS.

Technology is also playing a significant role. Functional imaging with novel PET promises to refine tumor targeting and treatment delivery as well as stratification of risk according to treatment response. Modern proton therapy has illustrated favorable

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QOL outcome gains in head and neck cancer and will likely continue to improve with the optimization and more widespread use of IMPT.

## IMPROVEMENTS IN INTENSITY-MODULATED RADIOTHERAPY TO IMPROVE SWALLOWING AND XEROSTOMIA OUTCOMES

With the implementation of IMRT for head and neck cancer in the 2000s, various dosimetric parameters to the pharyngeal constrictors and larynx have been correlated with aspiration risk, stricture risk, and patient-reported and observer-reported swallowing scores.<sup>1–3</sup> These have been applied successfully to reduce dysphagia in patients undergoing chemoradiation for head and neck cancer.<sup>4</sup> More recently, the mean dose to the floor of mouth (encompassing 3 suprahyoid and 2 extrinsic tongue muscles) was associated with an increased risk of aspiration.<sup>5</sup> In addition, a recent study from the MD Anderson Cancer Center (MDACC) noted that in addition to the pharyngeal constrictors, the mylo/geniohyoid complex, genioglossus, and anterior digastric muscle doses were associated with chronic radiation-associated dysphagia.<sup>6</sup>

Previously, parotid-sparing IMRT showed reduce xerostomia rates in multiple randomized studies.<sup>7,8</sup> More recently, submandibular-sparing techniques have been used to improve xerostomia outcomes.<sup>9</sup> In a series of 125 patients who underwent definitive chemoradiation with and without bilateral submandibular sparing for nodepositive oropharyngeal carcinoma, no locoregional failures occurred outside the treatment field and 2-year locoregional control rates were similar regardless of whether bilateral submandibular sparing was used. Patient-reported and observer-reported xerostomia scores were both significantly improved with submandibular sparing. Mean dose to the oral cavity, which contains minor salivary glands, also seems to be a significant predictor of patient-reported and observer-reported xerostomia, even after adjusting for parotid gland and submandibular gland doses.<sup>10</sup>

The emphasis on swallowing- and salivary gland–sparing IMRT seems to have yielded long-term, durable improvements in QOL. A series from the University of Michigan reporting on swallowing- and salivary organ–sparing chemoradiation for locally advanced, HPV-related oropharyngeal carcinoma showed long-term stable or improved QOL at 6 years compared with QOL prior to treatment and at 2 years of follow-up.<sup>11</sup>

# DEINTENSIFICATION OF RADIATION DOSE IN HUMAN PAPILLOMA VIRUS-RELATED OROPHARYNGEAL CARCINOMA

Conventional chemoradiation to 70 Gy with concurrent cisplatin<sup>12</sup> was established for locally advanced squamous cell carcinoma (SCC) of the head and neck in an era when much of the disease was related to alcohol and tobacco.<sup>13</sup> With the rapid rise in HPV-related oropharyngeal carcinoma, however, which is known to have a more favorable outcome, <sup>14,15</sup> there is a new focus on treatment deintensification. For example, multiple studies have indicated that a lower radiation dose may be sufficient for successful treatment given the compromised DNA repair capacity of HPV-related SCC tumor cells,<sup>16</sup> thus resulting in enhanced radiosensitivity. The pressing issue has been to identify means of de-escalating therapy without compromising disease control. **Table 1** lists several ongoing clinical trials assessing various deintensification regimens.

Differing approaches have emerged to identify suitable low-risk patients. One approach is to stratify patients according to response to initial treatment. Given the more robust response of HPV-related tumors to induction chemotherapy,<sup>17</sup> induction chemotherapy followed by lower-intensity chemoradiation to good responders is

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