Contemporary Radiotherapy in Head and Neck Cancer

Balancing Chance for Cure with Risk for Complication

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KEYWORDS

• Head and neck neoplasms • Radiotherapy • Intensity modulated radiotherapy • Radiation effects • Adverse effects • Dose fractionation

KEY POINTS

- Altered fractionation strategies improve outcome compared with conventional once-daily treatment of patients with locally advanced disease being treated with radiation therapy alone.
- Technological advances in diagnostic imaging and radiation delivery have improved the therapeutic ratio, with better disease delineation and sparing of normal tissues.
- Concurrent chemoradiation with intensity-modulated radiation therapy constitutes the standard nonsurgical therapy for locally advanced squamous cell head and neck cancer.
- Intensification strategies that add molecularly targeted agents to standard chemoradiation have resulted in increased toxicity but not improved efficacy to date.
- For patients who initially present with lymph node involvement, after chemoradiation PET-CT can distinguish those who do not require adjuvant neck dissection from those who do.

RADIATION THERAPY: BIOLOGIC BASIS AND FRACTIONATION

Approximately 49,000 cases of head and neck squamous cell cancer (HNSCC) are diagnosed in the United States annually; nearly 60% present with locally advanced but nonmetastatic disease.[1] Locoregional recurrence is the predominant pattern of failure from which most fatalities result. As a locoregional therapy, radiotherapy (RT) plays a primary role in treatment.

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Ionizing radiation causes cytotoxic effects via free radical–mediated DNA damage. This process precipitates a cascade of physicochemical reactions that lead to single-strand and double-strand DNA breaks, loss of reproductive integrity, and cell death. In the earliest days of RT, treatments often involved single large doses (fractions) of radiation.[2] Unfortunately, clinical responses were often accompanied by significant early and late toxicities. More protracted fractionated courses of RT were subsequently devised, which spread the treatment course out via the delivery of multiple smaller doses, with significantly reduced toxicity.

Four "Rs" underlying the radiobiology of fractionation have been described: repair of sublethal injury, cell repopulation, redistribution into more radiosensitive phases of the cell cycle, and reoxygenation.[3] These concepts have influenced the way RT is delivered for all types of cancer, including HNSCC. Nonmalignant cells more efficiently repair radiation-induced DNA damage than their malignant counterparts. Therefore, multiple radiation fractions give normal tissues time to repair sublethal damage, preferentially killing tumor cells. However, longer overall treatment times promote repopulation of both normal and cancerous cells. Consequently, as fractionated regimens become more protracted, they typically require higher total doses to achieve similar degrees of tumor control. Nonetheless, the delivery of each dose within a fractionated regimen redistributes more cells into the more radiosensitive G2/mitosis phase of the cell cycle, which enhances radiation-induced cell kill. One final advantage of fractionation is that it promotes tumor reoxygenation. Hypoxic cells are 2.5 to 3 times more resistant to a given dose of radiation than their well-oxygenated counterparts. Tumor hypoxia adversely affects the prognosis of head and neck cancer.[4–6]

Strategies to improve tumor control must be balanced against the ability of patients to tolerate the acute side effects of treatment and the potentially irreversible chronic toxicities that may subsequently occur. A conventional fractionation regimen used to treat HNSCC typically consists of once-daily 2 gray (Gy) fractions, five fractions per week, over 7 weeks, to a total dose of 70 Gy. This treatment is relatively well-tolerated with manageable mucositis; roughly one-third of patients experience some degree of grade 3 acute toxicity, and 2-year locoregional control (LRC) and overall survival (OS) rates are around 45%.[7] Altered fractionation regimens, such as hyperfractionation and accelerated fractionation, represent radiobiology-based approaches to improve treatment efficacy.

Hyperfractionation is designed to deliver higher total doses of RT to improve disease control without increasing late toxicity relative to conventional fractionation. Pure hyperfractionation regimens keep the same overall treatment time as conventional therapy but achieve higher doses via delivery of smaller, multiple daily fractions. Smaller individual doses of RT allow for preferential repair of sublethal DNA damage in normal tissues that are responsible for the development of late side effects compared with tumor cells. A commonly used regimen is 1.2 Gy twice daily, ten fractions per week, over 7 weeks, to a total dose of 81.6 Gy.

Pure accelerated regimens deliver the same or slightly reduced total dose of RT in a shorter overall treatment time relative to conventional fractionation. The goal of the condensed timeframe is to overcome tumor repopulation, which accelerates 3 to 4 weeks after RT initiation.[8] A typical regimen developed by the Danish Head and Neck Cancer Group (DAHANCA) uses 2 Gy fractions, six fractions per week, to a total dose of 70 Gy in 6 weeks. Hybrid regimens combine elements of hyperfractionation and acceleration. The concomitant boost regimen of the Radiation Therapy Oncology Group (RTOG) delivers a total dose of 72 Gy over 6 weeks, using 1.8 Gy daily fractions in the morning with the addition of a second 1.5 Gy fraction in the afternoon on the last 12 days of treatment to combat accelerated tumor repopulation.[9]