

New trends in radiotherapy for head and neck cancer

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Introduction

External beam radiation therapy has long been a major tool for treating early stage and locally advanced resectable and unresectable non-metastatic head and neck cancers. In general, conventional radiotherapy involves the delivery of fractionated target doses of 70 Gy or higher and is limited by the close proximity of the spinal cord, brain stem and parotid glands, which have lower radiation tolerance doses. Chronic complications, including mucosal fibrosis and atrophy, xerostomia, tooth decay, soft tissue necrosis, taste disturbance, and rarely osteonecrosis, are also limiting.

Attempts to improve both the efficacy and side-effect profile of radiotherapy led to the development of a number of alternative delivery schedules, employing different fractionation schedules, new techniques such as intensity-modulated radiotherapy (IMRT), and combination of radiotherapy with radiosensitizers, cytotoxic drugs and more recently with new molecular-targeted therapies.

Modified fractionated radiotherapy

Patients with locally advanced squamous cell carcinoma of the head and neck (HNSCC) who are not treated by primary surgery traditionally receive definitive radiotherapy. The conventional regimen—2 Gy per fraction delivered five times per week up to a total dose of 64–70 Gy—may offer an acceptable compromise between efficacy and safety. Over the past few decades, several approaches designed to increase the antitumor efficacy of radiotherapy for HNSCC have been tested, including regimens combining radiotherapy with concomitant chemotherapy and with radiosensitizers. Another tested approach, the use of an altered-fractionation regimen, aims to increase the dose intensity of radiotherapy by increasing the total radiation dose and number of fractions, and either decreasing the dose per fraction (i.e. hyperfractionation) or shortening the overall treatment time while using the same total dose, number of fractions and dose per fraction (i.e. accelerated fractionation) [1, 2]. Most altered-fractionation regimens use a combination of hyperfractionated and accelerated radiotherapy, and most of these have shown an improvement in locoregional control and a modest increase in survival rate. Although some authors have suggested that compared with the conventional radiotherapeutic regimen, accelerated radiotherapy increases acute toxicity, the severity and

incidence of late toxicity appear to be similar. Finally, a meta-analysis (J. P. Pignon, personal communication) of altered fractionated radiotherapy compared with conventional radiotherapy in 15 randomized trials regrouping 6515 patients showed a small but significant improvement in favor of altered fractionated radiotherapy for overall survival and local control, with an absolute benefit at 5 years of 3% and 6%, respectively.

Radio-chemotherapy combinations and combining radiotherapy with molecular-targeted therapies

Combining ionizing radiation with conventional cytotoxic agents, such as cisplatin, 5-fluorouracil (5-FU) or mitomycin C, has improved tumor control and overall survival in many cancer types including HNSCC and also nasopharyngeal carcinoma (NPC). Indeed, numerous randomized trials allowed the generation of evidence-based medicine level 1, showing the superiority of combined chemoradiation over radiotherapy alone, especially when chemotherapy was given concomitantly to irradiation. In HNSCC, a meta-analysis on chemotherapy, regrouping data for nearly 11 000 patients issued from 63 randomized trials, showed an absolute benefit of 4% at 5 years in overall survival in favor of chemotherapy ($P < 0.0001$). Most of the benefit was seen with concomitant radio-chemotherapy. An update of this meta-analysis was performed including 24 additional trials, which confirmed the magnitude of the benefit of concomitant chemotherapy (8% at 5 years). Interestingly, the benefit was observed in all the potential clinical situations, including postoperative radiotherapy [3, 4], definitive conventional radiotherapy and definitive modified fractionated radiotherapy [5]. The results showed that the optimal type of drug to be combined with irradiation included cisplatin–5-FU combinations or cisplatin alone given concomitantly with radiotherapy (absolute gain at 5 years 11%) [6, 7]. The benefit of adding cisplatin to radiotherapy has also been shown recently in a large randomized trial in the context of larynx preservation, which proved to be superior to an induction chemotherapy approach.

The effect of chemotherapy was also assessed in a meta-analysis based on individual patient data in NPC. Data from 11 randomized trials including 2722 patients comparing radiotherapy with chemoradiation (1979–2001) showed an absolute benefit of 6% at 5 years in overall survival in favor of

chemotherapy ($P < 0.0001$). Most of the benefit was also seen with concomitant radio-chemotherapy as compared with induction chemotherapy.

However, the addition of chemotherapy concomitantly with radiotherapy has also been shown to increase both acute and late toxicity [8]. Given this increase in toxicity, optimization is needed in order to improve efficacy and decrease toxicity, perhaps by using new radiation techniques such as IMRT (see below). A new generation of cytotoxic agents is also currently being tested in combination with ionizing radiation, including docetaxel, paclitaxel, gemcitabine or novel agents that are cytotoxic in hypoxic conditions (e.g. tirapazamine [9]). In a randomized phase II study, tirapazamine was used in combination with radiotherapy and cisplatin and compared with radiotherapy with cisplatin and 5-FU. Tirapazamine proved to be markedly superior to the 5-fluorouracil-containing arm, especially in tumors that proved to be hypoxic on positron emission tomography examination. Whether these new cytotoxic drugs may lead to superior results as compared with more conventional cytotoxic agents needs further investigations.

Molecular targeted therapy represents a way of further improving outcome with radiotherapy. Recent years have seen a dramatic increase in interest in so-called targeted therapies, and ways to maximize the potential of these compounds are currently being explored. Indeed, new generations of molecular targeting drugs have been combined with irradiation, showing promising results in preclinical studies. These drugs (inhibitors) have targeted angiogenesis, signal transduction pathways, growth factor receptors, farnesyl transferase and cell cycle regulators. These drugs have a relatively low toxicity profile distinct from conventional radiotherapy and chemotherapy, and have generally a relatively low antitumor activity on their own, pointing out the potential and the need to combine them with chemoradiation. Recently, a proof of principle has been obtained in a series of 424 patients with HNSCC, randomized to radiotherapy plus an antibody against the epidermal growth factor receptor (anti-EGFR, cetuximab) or to radiotherapy alone. Indeed, an improvement in both tumor control and survival was seen in patients receiving the combined treatment without an increase in acute mucosal toxicity [10, 11].

Intensity-modulated radiotherapy [12–14]

One of the more recent adaptations of radiotherapy technique is IMRT, in which multiple shaped radiation beams are modulated to produce highly conformal dose distributions. This approach enables the delivery of increased doses to tumor tissue while limiting the dose delivered to defined normal structures, especially to the salivary glands, auditory and optic apparatus, spinal cord, and larynx. The use of IMRT in oropharyngeal cancers has been reported in a number of small studies in patients with locally advanced disease. In these studies, salivary function was improved and locoregional control was excellent, although the follow-up is too short to

draw definitive conclusions. Thus, potential benefits of this approach are likely, but it should be pointed out that the limited mature clinical data available and the interpretation of those data that are available is complicated by the use of variable techniques. Indeed, IMRT is a relatively complex technique. Implementation of IMRT thus requires knowledge of set-up uncertainties, adequate selection of patients and delineation of target volumes based on clinical examination and multimodality imaging, appropriate specification and dose prescription regarding dose-volume constraints, and *ad hoc* quality control of both the clinical and physical aspects of the whole procedure.

Conclusions

In HNSCC, the development of altered fractionation regimens for the treatment of head and neck cancers has improved locoregional control. To date, the use of IMRT to deliver high tumor-targeted doses of radiotherapy represents an advance in treatment and one that is progressively being implemented. However, larger trials are still required to provide evidence for the use of IMRT compared with more conventional techniques.

Results from randomized phase III study and meta-analyses have demonstrated the clinical benefit of adding chemotherapy (cisplatin \pm 5-FU) to radiotherapy. Further optimization is needed to improve antitumor efficacy of these chemoradiation combinations, while decreasing toxicity. Finally, molecular-targeted therapy represents a way to further improve outcome with radiotherapy, as suggested in a recent randomized study combining an anti-EGFR (cetuximab) plus radiation.

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