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Controversy

The role of re-irradiation of secondary and recurrent head and neck carcinomas. Is it a potentially curative treatment? A practical approach

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ABSTRACT

Despite aggressive efforts to cure head and neck cancer patients, including altered fractionation and the addition of chemotherapy to radiation, locoregional recurrence remains a serious issue to face in clinical practice. Indeed, recurrent and second primary tumors occurring in previously irradiated area are common clinical challenge. Whenever possible, patients are advised to undergo salvage surgery. Nevertheless, few patients are suitable candidates for curative resection. In such cases, chemotherapy alone has traditionally been considered, with a poor response rate.

It has been questioned whether re-irradiation toxicity outweighs the potential benefits, considering that the median survival of re-irradiated patients marginally exceeds the benefits observed with chemotherapy alone. However, full-dose re-irradiation is a viable treatment option, offering long-term survival for selected patients.

Moreover, several prognostic factors should be considered for patients undergoing re-irradiation, such as basic patient characteristics, performance status, the location and extension of recurrent disease, patient co-morbidities, current speech and swallowing function, the interval from the initial radiation therapy to recurrence, previously received doses by critical structures and prior treatment toxicity. Nevertheless, several questions remain unanswered.

The purpose of this review is to evaluate the major issues in the field of re-irradiation regarding the current evidence. Therefore, the major selection criteria and new treatment strategies are discussed to define the ideal candidates to undergo re-irradiation and describe a practical approach to these patients.

Given the limited evidence in this field, the optimal treatment of recurrent and second primary cancers remains to be defined. Future prospective study of this approach is warranted.

Introduction

Despite recent advances in treatment [1–5] more than half of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) develop locoregional recurrence [6,7]. Unfortunately, locoregional relapses, and second primary tumors after definitive radiation treatment are common and often occur within high-dose treatment volumes, posing a great therapeutic challenge [7,8].

Whenever possible, surgery is proposed as a salvage strategy. Nevertheless, few patients are suitable candidates for curative resection. Currently, for patients with operable disease recurrence, surgical resection represents the standard of care, and 25% to 45% of patients experience long-term disease control [9]. When patients present with unresectable disease or are un-suitable candidates for surgery, three options can be discussed: supportive care only, palliative chemotherapy or radiotherapy (alone or combined with systemic therapy). The administration of a second course of radiation to tissues within a previous radiation field has been traditionally considered unsafe and has been avoided due to concerns regarding toxicity.

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Table 1
Selected chemotherapy (and targeted therapies) trials for locally recurrent and metastatic head and neck cancer.

Author	Type of study	Year	Number of patients		Regimen	Response rate (%)	Median survival (months)
Forastiere et al. [14]	Randomized	1992	277	87	Cisplatin + fluorouracil	32	6.6 NS
				86	Carboplatin + fluorouracil	21	5.0
				88	Methotrexate	10	5.6
Jacobs et al. [16]	Randomized	1992			Cisplatin + fluorouracil	32	5.7 NS
			249		Cisplatin	17	
					Fluorouracil	13	
Schrijvers et al. [17]	Randomized	1998	244	122	Cisplatin + fluorouracil + IFNα-2b	47	6.0 NS
				122	Cisplatin + fluorouracil	38	6.3
Forastiere et al. [13]	Randomized	2001	199	101	Cisplatin + paclitaxel (high dose)	35	7.6 NS
				98	Cisplatin + paclitaxel (low dose)	36	6.8
Soulieres et al. [18]	Phase II	2004	115		Erlotinib	4	6.0
Gibson et al. [15]	Randomized	2005	204	104	Cisplatin + fluorouracil	27	8.7 NS
				100	Cisplatin + paclitaxel	26	8.1
Burtness et al. [12]	Randomized	2005	117	57	Cisplatin + cetuximab	26	9.2*
				60	Cisplatin + placebo	10	8.0
Bourhis et al. [11]	Phase I/II	2006		53	Platinum + fluorouracil + cetuximab	36	9.8
Vermorken et al. [19]	Randomized	2008	442	220	Platin + fluorouracil	20	7.4
				222	Platin + fluorouracil + cetuximab	36	10.1**
Argiris et al. [10]	Randomized	2013	270	136	Docetaxel + placebo	6.2	6.0
				134	Docetaxel + gefitinib	12.5	7.3 NS

Abbreviation: NS, not statistically significant.
* ($p = 0.03$).
** ($p = 0.04$).

Thus, the standard treatment for these patients is systemic chemotherapy, which is widely used for palliation. However, chemotherapy alone yields a median survival between 5 and 9 months, and long-term survival is unfrequent (see Table 1) [10–18]. More recently, Vermorken et al. found in a recent randomized multicentric trial that the addition of cetuximab to platinum-based chemotherapy improved median survival to 10.1 months, compared to 7.4 months for those receiving chemotherapy without cetuximab [19]. Finally, although the risk of distant metastasis is high, most of these patients will die as a result of uncontrolled tumor growth at the primary site [7].

Re-irradiation: evidence and controversies

Salvage re-irradiation (unresectable disease)

The practice of full dose re-irradiation to a previously treated area was reported two decades ago by the Chicago group. The original treatment schedule included protracted radiotherapy, delivering 60 Gy over 11 weeks, with concomitant 5-fluorouracil (5FU) and hydroxyurea. This experience suggested that re-irradiation concomitantly with chemotherapy was feasible and could achieve long-term disease control in some patients, at the expense of a substantial rate of late toxicity [20,21]. These results were further confirmed in subsequent studies. De Crevoisier et al. reported the results of 169 patients with unresectable disease, presenting an overall survival rate of 21% at 2 years and 9% at 5 years [22].

More recently, the RTOG (Radiation Therapy Oncology Group) completed two phase II trials using split-course hyperfractionated re-irradiation and chemotherapy. RTOG study 96-10 used concurrent hydroxyurea and 5FU and achieved a median survival of 8.5 months and 2- and 5-year survival rates of 15.2% and 3.8%, respectively [23]. However, RTOG study 99-11 presented a median survival of 12.1 months and a 2-year survival rate of 25.9% using concurrent cisplatin and paclitaxel [24]. The acute toxicity in both studies was high. In another series reported by Langendijk and coworkers, 34 patients underwent re-irradiation with conventional fractionation, in which the majority of cases received doses of 60 Gy or more of radiation. The median overall survival was 13.2 months, with 2-year overall survival rates of 38% and 23% for patients with locoregional recurrence and for patients with second primary tumors, respectively [25]. In these studies, the 2-year survival rates appeared to be superior to those in series of patients treated with chemotherapy alone. However, whether these different results were due to treatment itself or from selection bias remains unanswered.

In a recent paper, Tortochaux et al. reported the results of a randomized phase III trial comparing re-irradiation (split-course hyperfractionated schedule) plus chemotherapy (5FU and hydroxyurea) to chemotherapy alone (methotrexate) in patients with recurrent or second primary HNSCC in a previously irradiated area [26]. The goal of the study was to evaluate the potential benefit of concurrent re-irradiation plus chemotherapy versus a single chemotherapeutic agent. Premature discontinuation of the trial did not allow firm conclusions to be drawn. However, there was no suggestion of an improvement in overall survival with re-irradiation compared to chemotherapy alone.

Currently, there are no other randomized data that suggest optimal approaches for patients with recurrent or second primary HNSCC in previously irradiated areas. In fact, the RTOG started a similar randomized phase III trial, but it was closed early due to lack of recruitment. Thus, the evidence for offering re-irradiation as a curative treatment has come mainly from retrospective and phase II trials [20–25].

Postoperative re-irradiation

Although many investigators believe that re-irradiation is only necessary in the setting of gross macroscopic disease, the effectiveness of postoperative re-irradiation after salvage surgery has been addressed. A phase II study conducted at the Institute Gustave-Roussy reported the long-term results of re-irradiation with concomitant chemotherapy following salvage surgery in patients who had positive margins and/or lymph node involvement with extracapsular extension. These authors reported 4-year survival of 43% and 5-year disease survival of 26% [27]. Considering these results, the Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) and the Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) conducted a phase III phase randomized trial to address this issue [28]. Previously irradiated patients, were randomized to observation or re-irradiation (60 Gy over 11 weeks; 2 Gy/day) with chemotherapy (concomitant 5FU + hydroxyurea) after