Journal of BUON **14:** 361-373, 2009

REVIEW ARTICLE

Radiotherapy and chemotherapy in locally advanced head and neck squamous cell carcinoma

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Summary

Throughout the past two decades the efforts to improve the efficacy of treatment for locally advanced head and neck squamous cell carcinoma (HNSCC) have led to increased use of multimodality approaches combining surgery, radiotherapy (RT), and chemotherapy (CT). Conventional RT, a standard approach for locoregionally advanced disease, was associated with unsatisfactory results, thereby, a greater understanding of radiobiology led to the development of two classes of altered radiation fractionation schedules incorporating hyperfractionation (HF) and acceleration in the management of advanced HNSCC. Randomized controlled trials and meta-analyses demonstrated that for patients with locally advanced HNSCC major improvements in locoregional control (LRC) at high level of evidence can be achieved by accelerated fractionation (AF) and HF. For these patients, overall survival (OS) may be improved at high level of evidence by HF delivered with increased total dose.

CT represents an important component of multimodality treatment approach for locally advanced HNSCC with concurrent addition of CT to RT being the most significant method for improving head and neck cancer (HNC) outcome. Several randomized studies and meta-analyses on the administration of concurrent chemoradiotherapy (CCRT) demonstrated clear evidence that CCRT provides a substantial and statistically significant improvement in survival and locoregional control, as compared to RT alone. CCRT is now a standard treatment approach for patients with locally advanced HNSCC. CCRT has been also shown to allow organ preservation in almost two thirds of patients without affecting survival. Recently, strong evidence for an improved outcome for high-risk resected patients has been shown by the use of adjuvant CCRT.

Key words: adjuvant concurrent chemoradiotherapy, altered fractionation, chemotherapy, concurrent chemoradiotherapy, head and neck cancer, radiotherapy

Introduction

HNSCCs are frequent tumors with an estimated annual global incidence of more than 550,000 cases diagnosed worldwide [1]. HNSCCs mainly include cancers of the oral cavity, pharynx and larynx and are more frequently diagnosed as locally or locoregionally advanced disease. According to the Tumor Nodes Metastases (TNM) stage classification established by International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) [2], patients with HNSCCs may be assigned to 4 different classes of prognosis with different risk of failure (stage I-IV). Also, there is further classification of stage IV: tumors that are locally advanced but surgically resectable and therefore salvageable are classified as stage IVA; tumors which are locally advanced and surgically unresectable but potentially treatable are classified as stage IVB; and patients with distant metastatic disease that is incurable and therefore only suitable for palliative treatment are classified as stage IVC.

Several methods for the treatment of locally advanced HNSCC are employed including surgery, RT and CT. Irrespectively of the progress in surgical techniques and in RT delivery, and the advent of new cytotoxic drugs, treatment outcomes are still characterized by 3 main features: LRC remains unsatisfactory, with 3-year rates rarely exceeding 50-60%; treatment failure

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Received 19-11-2008; Accepted 21-12-2008

due to distant metastases should not be underestimated, and the improvements in LRC and disease-free-survival (DFS) rates accomplished by the novel approaches are obtained at the price of increased acute and late toxicity [3]. In theory, the choice of the best treatment in HNSCC patients with advanced disease should be made in an attempt to obtain an increased survival (improved locoregional control, reduced probability of distant metastases and second primary), an increased organ function preservation in resectable and unresectable tumors, and an increased therapeutic ratio (cure/toxicity ratio) [4].

Altered fractionation and RT-CT combinations are strategies shown in large randomized trials to lead to clinically important improvements in outcome of patients with locally advanced HNSCC.

Radiotherapy

Conventional radiotherapy

In RT, conventional treatment practice is the outcome of empirical development and optimization during one century of x-rays and constitutes the solid base for further development [5]. Conventional RT varies greatly in different countries, but the administration of 1.8 to 2 Gy per fraction, five times per week, may be regarded as standard treatment practice [5,6]. Considering the results of conventional RT with total dose of 70 Gy as definitive treatment option (locoregional failure seen in more than 30-50% of cases and ultimate 30% 5-year survival rate), it was obvious that large primary tumors and/or advanced neck disease demanded delivery of large total doses in order to enhance the tumor control probability [7].

Rational modification of radiation fractionation regimens has been a subject of intensive clinical investigations for more than 3 decades, attempting to improve the outcome of patients with locally advanced HNSCC.

Altered fractionation

The two prototypes of altered radiation fractionation regimens are HF and AF. HF implies the administration of a larger number of smaller doses per fraction in approximately the same overall time as in conventional therapy and represents one of the most interesting modifications of conventional fractionation (CF). HF is generally expected to allow an escalation of total dose, thereby increasing tumor control rate, without the risk of late complications [5,8]. The groups that explored HF tried to exploit the radiobiological hypothesis that late-responding tissues are more sensitive to change in dose per fraction than early-responding tissues [9]. There are several randomized trials exploring HF [10-13].

In the Rio de Janeiro trial [10] carried out on 98 patients with stages III and IV oropharyngeal squamous cell carcinoma (SCC), HF consisted of 64 fractions of 1.1 Gy given twice-a-day to a total dose of 70.4 Gy with a minimal interfraction interval of 6 h. CF was delivered in 33 fractions of 2 Gy to a total dose of 66 Gy. There was a significant improvement in the response rate at the primary site in the HF arm (84 vs. 64%; p=0.02). OS rate at 3.5 years was 27% and 8% for patients randomized to HF and CF, respectively (p=0.03).

In the Toronto trial reported by Cummings et al. [11], 331 patients with locoregionally advanced SCC of the larynx, oro- or hypopharynx were randomized to HF or CF. The conventional regimen of the Princess Margaret Hospital study employed larger doses per fraction than CF in the US or Germany. A total dose of 51 Gy, 2.55 Gy per fraction, 5 daily fractions per week over 4 weeks was given as conventional regimen. The HF in this trial consisted of 58 Gy delivered in 1.45 Gy per fraction over 4 weeks. The 5-year local relapse rate was reduced in the HF (41%) compared to the CF arm (49%) (p=0.082). Survival (40 vs. 30%) was also improved with HF compared to CF arm (p=0.069).

The European Organization for Research and Treatment of Cancer (EORTC) 22791 protocol [12] is considered one of the most important trials performed in radiation oncology. In this trial on 356 patients suffering from T2 and T3 oropharyngeal carcinoma, once daily CF of 70 Gy in 35-40 fractions within 7-8 weeks was compared to HF of 80.5 Gy in 7 weeks, applying 2 fractions of 1.15 Gy per day with 4 to 6 h gap between fractions. The local control was significantly higher (p=0.02) after HF compared with CF. At 5 years, 59% of patients were local disease-free in the HF arm compared to 40% in the CF arm. In addition, a trend to improved OS after HF was observed (p=0.08).

The largest prospective randomized trial undertaken to compare standard fractionation RT against HF and AF with split course and accelerated RT with concomitant boost in the management of patients with advanced HNSCC was RTOG trial 9003 [13]. In this 4-arm trial of 1073 patients with locally advanced HNSCC the conventionally fractionated RT schedule was 70 Gy in 7 weeks (one fraction of 2 Gy per day, 5 fractions per week). The HF treatment schedule was 79.2 Gy in 6.5 weeks (2 fractions of 1.2 Gy per day, 10 fractions per week with interfraction interval of at least 6 h). The results of this study showed that the locoregional control was significantly increased with increasing

Table 1. Radiation-induced morbidity in randomized phase III trials exploring hyperfractionation

Trial [Reference]	*Patients n*	*Side effects*
Pinto et al. [10] (Rio de Janeiro trial) 1991	98	Earlier onset of acute toxicities represented by erythema to confluent mucositis in the oropharynx and oral mucosa and by erythema to moist desquamation in the skin with HF; late complications, no details
Cummings et al. [11] (Toronto trial) 2007	331	Reversible acute toxicity increased with HF; the overall 5-year rate of grade 3-4 late toxicity for the CF was 10.5% compared to 7.7% in the higher dose HF arm
Horiot et al. [12] EORTC trial 22791 1992	356	Objective acute mucosal reactions more severe in HF arm (p=0.01); no difference in late complication rate
Fu et al. [13] RTOG trial 9003 2000	1073	Significantly increased grade 3 or worse acute side effects with HF ($p < 0.0001$); no difference in the frequency of grade 3 or worse late effects

HF: hyperfractionation, CF: conventional fractionation, EORTC: European Organization for Research and Treatment of Cancer, RTOG: Radiation Therapy Oncology Group

the total dose without changing the overall time using HF (p=0.045). There was no increase in OS with HF.

Concerning the treatment-related toxicity, all 4 studies showed that HF induced more severe acute mucositis but did not result in detectable increase in late morbidity (Table 1).

AF is characterized by a reduction of overall treatment time (OTT) with or without changes in dose per fraction and with or without total dose reduction [6]. AF is expected to obtain increased level of tumor control probability by counteracting the accelerated tumor clonogen proliferation during irradiation using shortened OTT [14]. Pure AF regimens reduce OTT without concurrent changes in the fraction size or total dose. The Danish Cooperative Group [15] and a Polish Cooperative Group [16] both carried out studies of 6 instead of 5 daily fractions per week, to a total dose of 66 Gy. The additional weekly fraction was delivered on Saturday or as a second daily fraction during the week (Table 2). These two large trials found that 1-week reduction in the OTT led to a significant increase in the LRC rate, but without significant effect on survival (Table 2). In both studies more severe acute reactions were produced by AF but no difference in late complications was observed except for telangiectasia in the Polish study ($p < 0.001$).

In the randomized trial on 7-day continuous accelerated irradiation (CAIR) [17] conducted in Poland on 100 patients with HNSCC, the acceleration of 2 weeks resulted in significant improvement in 3-year local tumor control ($p < 0.0001$) and OS ($p < 0.0001$) (Table 2). The incidence of severe confluent mucositis was 2 times

Table 2. Phase III trials of pure accelerated fractionation with head and neck cancer

Trial [Reference]	*Dose per fraction (Gy)*	*Fractions per day*	*Total dose (Gy)*	*OTT (weeks)*	*Tumor response*
Danish Cooperative Group trial [15], 2000	AF: 2.0	AF: 1	AF: 66	AF: 6.0	5-year LRC, 66%
(n=1485)	CF: 2.0	CF: 1	CF: 66	CF: 7.0	5-year LRC, 57%
Various sites, all stages					LRC significantly better with AF (p=0.01); no difference in OS
Polish Cooperative Group trial [16], 2000	AF: 2.0	AF: 1-2	AF: 66	AF: 5.5	LRC significantly higher with AF (p=0.03); no difference in OS
(n=395)	CF: 2.0	CF: 1	CF: 66	CF: 6.5	
Laryngeal cancer, T1-3, N0					3-year LC, 82%
CAIR trial [17], 2000	AF: 1.8-2.0	AF: 1	AF: 70	AF: 5.0	3-year OS, 78%
(n=100)	CF: 1.8-2.0	CF: 1	CF: 70	CF: 7.0	3-year LC, 37%
					3-year OS, 32%
Various sites, T2-4, N0-1					LC significantly higher with AF ($p < 0.0001$); OS significantly higher with AF ($p < 0.0001$)

OTT: overall treatment time, AF: accelerated fractionation, LRC: locoregional control, CF: conventional fractionation, OS: overall survival, CAIR: continuous accelerated irradiation, LC: local control

higher in the AF than in the control group (62 vs. 26%). There were no severe late reactions in CF group compared to overall rate of 10% in the AF group.

Hybrid AF also reduces the OTT but with changes in other variables such as fraction size, total dose and time distribution. Three types of hybrid AF have been tested in randomized trials (Table 3). Type A consists of an intensive short course of treatment in which the OTT is much shortened with a substantial decrease in total dose. Continuous hyperfractionated accelerated RT (CHART) vs. CF was tested in a randomized multicentre trial carried on 918 patients with HNSCC [18]. The CHART schedule was the most drastically accelerated regimen with OTT shortened for 4.5 weeks. There was also the greatest total dose reduction in the CHART arm compared to CF arm (18%) (Table 3). Despite the reduction in total dose from 66 to 54 Gy, similar local tumor control and OS were achieved by CHART as compared to conventional RT (Table 4). Acute reactions were more severe with CHART. Confluent mucositis occurred in 73% of the CHART cases compared to 43% of those treated with CF. On the other hand, total dose reduction was associated with reduced late treatment-related morbidity.

In a phase III randomized Groupe Oncologie Radiotherapie Tete et Cou (GORTEC) trial 94-02 [19], a 3.5-week acceleration regimen with a dose reduction of only 7 Gy (10%) was assessed predominantly in patients with locally advanced oropharyngeal carcinoma (Table 3). There was a significant difference in LRC rate favoring the AF arm (p=0.01), but the OS was not statistically different between treatment modalities (Table 4). Acute mucositis was more severe in the AF arm with feeding tube more frequently required (89% of cases; p= 0.001). A comparable proportion of late toxic effects was seen in both arms with a median follow-up of 28 months.

In type B, that is AF with split course, and in type C, that is AF with concomitant boost, the duration of treatment is more modestly shortened but the total dose or fraction size is kept in the same range as conventional treatment. Split-course AF was tested in the EORTC randomized trial 22851 [20] and in the RTOG trial 9003 [13] (Table 3). In the EORTC trial 22851 split-course scheme consisted of a first course delivering 28.8 Gy in 18 fractions and 8 days, then 12-14 day split, and the second course from day 21 delivering 43.2 Gy in 27 fractions and 17 days resuming the whole treatment to 72 Gy in 5 weeks (Table 3). This 3-times-a-day regimen provided 2 weeks treatment acceleration and a 3% total dose increment. There was a significant improvement in LRC with AF (p=0.02; Table 4). Acute morbidities (including death from radiation) were increased in the AF arm and late severe functional damage (including 2 cases of radiation-induced myelitis) occurred in 14% of patients treated with AF. The split-course regimen assessed in RTOG trial 9003 had 1-week acceleration and 4% reduction in total dose (Table 3). Patients treated with split-course AF had similar outcome to those treated with CF (Table 4). In the group treated with split-course AF significantly higher frequency of acute side effects but not of late toxic effects was reported [13].

Concomitant boost schedule, being one of the arms in RTOG 9003 4-arm study, characterized by de-

Table 3. Treatment parameters in hybrid accelerated fractionation explored in phase III trials

Trial [Reference]	*Total dose (Gy)*	*Dose per fraction (Gy)*	*Fractions per day*	*OTT (weeks)*
Accelerated fractionation with total dose reduction (type A)				
Dische et al. [18] CHART, 1997	54.0	1.5	3	2.0
Bourhis et al. [19] GORTEC 94-02, 1997	63.0	2.0	2	3.3
Accelerated fractionation with split course (type B)				
Horiot et al. [20] EORTC 22851, 1997	72.0	1.6	3	5.0
Fu et al. [13] RTOG 9003, 2000 Split-course	67.2	1.6	2	6.0
Accelerated fractionation with concomitant boost (type C)				
Fu et al. [13] RTOG 9003, 2000 Concomitant boost	72.0	1.8 (basic) 1.5 (boost)	1 for the first 18 days 2 for the last 12 days	6.0

OTT: overall treatment time, CHART: continuous hyperfractionated accelerated radiotherapy, GORTEC: Groupe Oncologie Radiotherapie Tete et Cou, EORTC: European Organization for Research and Treatment of Cancer, RTOG: Radiation Therapy Oncology Group

Table 4. Response to treatment in phase III trials of hybrid accelerated fractionation

Trial [Reference]	*Tumor response*
Accelerated fractionation with total dose reduction (type A)	
CHART [18] (n=918)	No difference in LRC or OS between AF and CF
GORTEC 94-02 [19] (n=268)	2-year LRC 58% with AF vs. 34% with CF (p<0.01); no difference in OS
Accelerated fractionation with split course (type B)	
EORTC 22851 [20] (n=500)	5-year LRC 59% with AF vs. 46% with CF (p=0.02); trend to higher 5-year DFS with AF (p=0.06); no difference in OS
RTOG 9003 [13] (n=1073) Split-course arm vs. CF arm	No difference in LRC and OS between AF with split-course and CF
Accelerated fractionation with concomitant boost (type C)	
RTOG 9003 [13] (n=1073) Concomitant boost arm vs. CF arm	2-year LRC 54.5% with AF with CB vs. 46% with CF (p=0.050); 2-year DFS 39% vs. 32% with CF (trend to higher 2-year DFS with AF with CB (p=0.054); no difference in OS

CHART: continuous hyperfractionated accelerated radiotherapy, LRC: locoregional control, OS: overall survival, AF: accelerated fractionation, CF: conventional fractionation, GORTEC: Groupe Oncologie Radiotherapie Tete et Cou, EORTC: European Organization for Research and Treatment of Cancer, DFS: disease-free survival, RTOG: Radiation Therapy Oncology Group, CB: concomitant boost

livering the boost (12 fractions) as second-daily treatment during the basic wide field irradiation, resulted in shortening the OTT to administer 72 Gy from 7.5 to 6 weeks (Table 3). The results of RTOG trial 9003 published by Fu et al. [13] in 2000 revealed that AF with concomitant boost yielded a significantly better LRC than standard RT (p=0.05) and a trend toward improved DFS (Table 4). OS was instead similar in all of the groups. Compared to the CF arm, AF with concomitant boost arm had significantly higher grade 3 or worse acute side effects ($p < 0.0001$) and significantly increased grade 3 or worse late side effects ($p < 0.011$).

However, the wide spectrum of fractionation parameters used in hyperfractionated and/or accelerated regimens makes comparison of treatment results difficult in relation to changes in treatment parameters i.e. total doses, doses per fraction, interfraction intervals and OTT [21].

A metaanalysis undertaken by MARCH (Meta-Analysis of Radiotherapy in Carcinomas of the Head and Neck) Collaborative Group [22] and aimed to assess whether different types of altered fractionated RT in HNSCC could improve survival compared with conventional RT, included findings of 15 trials with 6515 patients. This metaanalysis of updated individual patient data showed an improvement of 6.4% of LRC (from 46 to 53%, p<0.0001), and an improvement of 3.4% of OS (from 36 to 39%, p<0.03) with altered fractionation. The benefit in OS was significantly higher with HF (8% at 5 years) than with accelerated RT. The results of this metaanalysis suggest that altered fractionated RT improves survival in patients with HNSCC. The authors pointed out that the comparison of different types of altered RT suggests that HF has the greatest benefit. The advantage of HF was also confirmed in the German metaanalysis by Budach [23]. The findings of this metaanalysis based on published data suggest that, among different types of altered RT, HF obtained better 2-year OS than conventional RT with a significant benefit of 12 months ($p < 0.001$).

According to the results of randomized trials exploring altered fractionation regimens and considering the results of the 2 metaanalyses, evidence-based medicine showed that acceleration of radiation of 1 week without dose reduction and HF are consistently better than CF for LRC of intermediate to advanced carcinomas without an increase in late toxic effects (National Cancer Institute [NCI] level 1 of evidence supporting recommendation) [4]. It must be mentioned that, although improvement in patients' survival has not been consistent, a better benefit in OS was mainly shown with HF.

Chemotherapy

The integration of CT as treatment option into combined modality approaches has been another step investigated in the goal to improve outcomes in the proportion of patients with unresectable and/or inoperable, locally advanced HNSCC characterized with poor LRC rates, long-term DFS and OS rates when treated with "traditional" only one-day fractionation RT. The

rationale for chemo-RT association was not only to increase the probability of LRC using the concept of additivity whereby the two modalities act independently to increase total cell kill and also by amplifying the RT efficacy by using together two different tumoricidal agents where the CT enhances the radiation response in a supra-additive way, but also to eradicate systemic micrometastases using the concept of spatial cooperation and consequently to reduce the incidence of distant metastases that can account for up to 30% in some high-risk patients. CT may be given as induction, delivered prior to definitive locoregional treatment, as concurrent given concomitantly with conventionally fractionated RT (CCRT), as intensified concurrent given concomitantly with altered fractionated RT, or as sequential treatment approach utilizing both induction chemotherapy (ICT) and CCRT.

Concurrent chemoradiotherapy

In the late 1970s, investigations of a number of cytotoxic drugs enabled oncologists to obtain the first promising response rates for HNSCC. The most widely investigated drugs combined concurrently with RT were platinum derivatives and 5-fluorouracil (5-FU). The most significant potential mechanisms of enhanced activity of RT when combined concurrently with platinum derivatives and 5-FU are: decrease in accumulation or inhibition of repair of sublethal damage; inhibition of repair of potentially lethal damage; induction of tumor reoxygenation by reducing tumor burden; selective cytotoxicity and/or radiosensitization of hypoxic cells; synchronization and redistribution of tumor cells into the more sensitive cell-cycle phase, and increase of apoptosis [24,25].

At least 7 prospective phase III trials comparing platinum-based CCRT vs. RT alone have been reported [26-33].

Merlano et al. [26] reported 5-year update of a randomized trial comparing alternating RT and CT vs. RT alone in the treatment of locally advanced inoperable HNSCC (Table 5). The 5-year OS, progression-free survival (PFS) and locoregional relapse-free survival (LRRFS) were significantly better in the combined-treatment group compared with the RT-only group (p=0.01, p=0.008, and p=0.038, respectively) (Table 6). The investigators noted that the superiority of alternating CT and RT over RT alone in treating unresect-

Table 5. Treatment parameters in phase III trials comparing concurrent chemoradiotherapy vs. radiotherapy alone

Authors [Reference]	*Patient population*	*Therapy regimens*
Merlano et al. [26] 1996	n=157 Untreated, unresectable HNSCC, various sites	60 Gy in 3 courses of 20 Gy each, given in 2.0 Gy/fx/d, 5 fx/wk during weeks 2-3, 5-6, and 8-9, plus 4 courses of cisplatin (20 mg/m^2) and 5-FU (200 mg/m^2), given daily for 5 consecutive days during weeks 1, 4, 7, and 10 vs. RT alone (70 Gy, 2.0 Gy/fx/d, 5 fx/wk)
Adelstein al. [27] 2003	n=295 Various sites, 96% of patients with stage IV disease	70 Gy given with 2.0 Gy/fx/d, 5 fx /wk plus concurrent cisplatin 100 mg/m^2 iv on days 1, 22 and 43, or the same RT regimen with 3 courses of a 4-day continuous infusion of 5-FU 1,000 mg/m^2/d, with cisplatin bolus injection of 75 mg/m^2 on day 1, given every 4 weeks vs. RT alone
Denis et al. [28] 2004	n=226 SCC of the oropharynx, stage III-IV	70 Gy given with 2.0 Gy/fx/d plus 3 courses starting on days 1, 22, and 43 of a 4-day continuous infusion of 5-FU 600 mg/m^2/d, with carboplatin bolus injection of 70 mg/m^2/d for 4 days vs. RT alone
Jeremic et al. [29] 2000	n=130 Various sites, stage III-IV	77 Gy given in 1.1 Gy/fx/twice daily plus cisplatin 6 mg/m^2/d vs. RT alone
Staar et al. [30] 2001	n=240 SCC of oropharynx and hypopharynx, stage III-IV	69.9 Gy over 5.5 weeks (1.8 Gy/fx/d for 3.5 weeks, then individual fx of 1.8 Gy and 1.5 Gy daily for 2 weeks plus carboplatin 70 mg/m^2/d and 5-FU (600 mg/m^2/d) for 2 cycles of 5 days vs. RT alone
Wendt et al. [31] 1998	n=270 Various sites, stage III-IV	70.2 Gy given with 1.8 Gy/fx/twice daily in 3 courses with 10-day break plus cisplatin 60 mg/m^2, 5-FU 350 mg/m^2 by i.v. bolus, and LV 50 mg/m^2 by i.v. bolus given on day 2, and 5-FU 350 mg/m^2/24 hour by continuous infusion and LV 100 mg/m^2/24 hours by continuous infusion given from day 2 to 5 starting on days 22 and 44 vs. RT alone
Brizel et al. [32] 1998	n=122 Various sites, T2-4 N0-3	70 Gy given with 1.25 Gy/fx/twice daily (7-10 days break after 40 Gy) plus cisplatin 12 mg/m^2/d and 5-FU 600 mg/m^2/d in week 1 and 6 vs. RT alone with 75 Gy as 1.25 Gy/fx/twice daily

HNSCC: head and neck squamous cell carcinoma, fx: fraction, d: day, wk: per week, 5-FU: 5-fluorouracil, RT: radiotherapy, SCC: squamous cell carcinoma, i.v.: intravenous, LV: leucovorin

Table 6. Treatment results in phase III trials comparing concurrent chemoradiotherapy vs. radiotherapy alone

Authors [Reference]	*Tumor response*	*Complications*
Merlano et al. [26]	5-year LRRFS, 64% vs. 32% (p=0.038); 5-year PFS, 21% vs. 9% (p=0.008); 5-year OS, 24% vs. 10% (p=0.01)	No significant difference in acute toxic effects; late toxic effects not reported
Adelstein al. [27]	3-year DSS, 51% in CCRT arm vs. 33% in RT arm (p=0.01); 3-year OS, 37% in CCRT arm vs. 23% in RT arm (p=0.014)	Grade 3 or worse acute toxic effects, 89% in CCRT arm vs. 52% in RT arm ($p < 0.0001$); late toxic effects not reported
Denis et al. [28]	5-year LRC, 48% vs. 25% (p=0.0002); 5-year SDFS, 27% vs. 15% (p=0.01); 5-year OS, 22% vs. 16% (p=0.05)	No significant difference in grade 3-4 acute complications; no significant difference in grade 3-4 late toxic effects
Jeremic et al. [29]	5-year LRPFS, 50% vs. 36% (p=0.04); 5-year PFS, 46% vs. 25% (p=0.007); 5-year DMFS, 86% vs. 57% (p=0.001); 5-year OS, 46% vs. 25% (p=0.008)	No significant difference in acute toxic effects with exception of leucopenia (p=0.006); no difference in late toxic effects
Staar et al. [30]	2-year OS, 48% vs. 39% (p=0.11); 2-year LC, 51% vs. 45% (p=0.14); worse LRC in patients receiving CCRT (p=0.007)	Grade 3-4 mucositis, 68% vs. 52% (p=0.01); feeding tube dependency, 51% vs. 25% (p=0.02)
Wendt et al. [31]	3-year LRC, 36% vs. 17% ($p < 0.004$); 3-year OS, 48% vs. 24% ($p < 0.0003$)	Grade 3-4 acute mucositis, 38% vs. 16% ($p < 0.001$); no significant difference in late toxic effects
Brizel et al. [32]	3-year LRC, 70% vs. 44% (p=0.01); 3-year RFS, 61% vs. 41% (p=0.07); 3-year OS, 55% vs. 34% (p=0.07)	Similar mucositis; increased enteral feeding and sepsis with combination therapy; no difference in late toxic effects

LRRFS: locoregional relapse-free survival, PFS: progression-free survival, OS: overall survival, DSS: disease-specific survival, CCRT: concurrent chemoradiotherapy, RT: radiotherapy, LRC: locoregional control, SDFS: specific disease-free survival, LRPFS: locoregional progression-free survival, DMFS: distant metastases-free survival, LC: local control, RFS: relapse-free survival

able HNSCC seen at 3 years was confirmed at 5 years.

In the Intergroup phase III study (Southwest Oncology Group [SWOG] and Eastern Cooperative Oncology Group [ECOG]) [27] for locally advanced and unresectable HNSCC, patients were randomized into 3 arms: 1) single-agent cisplatin every 3 weeks during RT; 2) cisplatin+5-FU with RT; or 3) RT alone. All patients were treated with conventionally fractionated RT (Table 5). Statistically significant difference favoring CCRT was observed only between cisplatin plus RT and RT alone (p=0.016) (Table 6).

Results of the GORTEC randomized phase III trial 94-01 [28] (Table 5) of CCRT with carboplatin and 5-FU in locally advanced oropharyngeal carcinoma showed statistically significant improvement of 5-year LRC, OS and specific disease-free survival (SDS) (p=0.002, p=0.05, and 0.01, respectively) (Table 6).

In a study of HF (Table 5) Jeremic et al. [29] reported a significant improvement in 3-year LRC, OS and distant-metastases-free survival (DMFS) with HF and concurrent low-dose daily cisplatin as compared with HF alone. These authors also reported similar frequency of acute mucositis and late complications in both arms (Table 6).

In the multicentric randomized German trial conducted by German Cooperative Group [30], a concomitant boost AF alone was compared with the same RT regimen plus carboplatin and 5-FU (Table 5). There was significantly worse LRC in patients receiving chemo-RT ($p < 0.007$) and 2-year OS was not significantly improved (Table 6). The authors concluded that the efficiency of intensified CCRT was less than expected when compared to RT alone.

Wendt et al. [31] reporting the results of a regimen consisting of split-course altered fractionation plus CT (Table 5) concluded that CCRT offered significantly improved 3-year LRC and OS rate ($p < 0.004$ and $p < 0.0003$, respectively). Acute reactions were more pronounced in the CCRT arm ($p < 0.001$; Table 6).

Brizel et al. [32] randomly assigned 122 patients with advanced HNSCC to receive split-course hyperfractionated schedule in combination with cisplatin and 5-FU or to hyperfractionated RT alone (Table 5). This trial also showed better LRC achieved by CCRT but without any improvement in OS (Table 6).

Consistently, CCRT trials report an increased incidence of grade 3 and 4 acute toxicities with mucositis and dermatitis being the most prominent. On the other hand, severe long-term side effects are not increased in comparison to radiation alone, and virtually all patients

recover from the intense treatment [33].

Many metaanalyses have been conducted to show whether chemo-RT association is better than RT alone as concerns LRC and survival [23,34-38].

The results of metaanalysis of the published data from 54 randomized controlled trials of CT in HNSCC reported by Munro [34] in 1995 suggested that single-agent CT given concurrently with RT had the highest benefit with increased survival by 12%.

In the metaanalysis of El-Sayed and Nelson [35] on 42 prospective and properly randomized trials, a statistically significant improvement in survival was also found for the concurrent use of CT and local definitive treatment.

The largest metaanalysis performed by the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group and published by Pignon et al. [36] in 2000, evaluated individual patient data from 63 randomized trials excluding trials on nasopharyngeal carcinoma. This metaanalysis confirmed the superiority of the overall use of CT with 5% improvement in 5-year OS. The estimated increase in survival was highest with CCRT (8% at 5-years; $p < 0.0001$). In neoadjuvant or adjuvant settings the overall effect of adding CT was not statistically significant. There was also an evident benefit when cisplatin was used in the combined approach. In patients over 70 years the benefit was less evident. In the updated meta-analysis published in 2004 [37], 24 new trials, most of them on CCRT, were included, totalizing 87 trials and 16,000 patients. The update confirmed survival benefit of 8% at 5 years ($p < 0.0001$) of CCRT. This updated analysis also confirmed the higher magnitude of the benefit for platinum-based CT. A decreasing effect of CT with age was also shown ($p=0.01$). The OS gain was better for CCRT with altered fractionation compared with CCRT with conventional fractionation, indicating that alteration of fractionation might boost the effect of chemo-RT.

Browman et al. [38] reported a metaanalysis including 18 trials with 3,192 patients, in which CCRT was compared to RT alone. This metaanalysis also showed the superiority of CCRT ($p < 0.00001$). Only platinum-based CT plus RT was highly significant ($p < 0.0001$).

The German metaanalysis carried out on 32 trials with a total of 10,225 patients and based only on the published data, suggests that, considering only CCRT without prolonged OTT, an absolute survival gain of 13-15% at 2 years with respect to conventional RT can be obtained [23].

During the past 25 years, the extensive research of the influence of the addition of CT to RT on OS resulted in confirmation that only CCRT as definitive treatment for patients with locoregionally advanced HNSCC has succeeded to improve outcomes. The results of both single-institutional and multi-institutional randomized phase III trials comparing RT alone to CCRT, as well as several metaanalyses, seem to be quite sufficient to make evidence-based recommendations supporting RT and concurrent platinum-based chemoradiotherapy as a standard of care in patients with locally advanced HNSCC (NCI level 1 of evidence supporting recommendation) [33].

Organ preservation in resectable locally advanced HNSCC

A critical point of research in HNSCC was to evaluate whether chemo-RT association can offer potential for organ-function preservation for patients with advanced disease of the larynx and hypopharynx without compromising OS.

ICT, the use of systemic CT before definitive surgery and/or RT, has been a well-studied option in the management of HNSCC for the last 25 years. In the 1980s, the demonstrated efficacy of ICT in patients with HNSCC with regard to larynx preservation, suggesting that surgery could be omitted in responding patients without compromising survival [39,40], led to 3 prospective randomized trials [41-43]. All of them were two-arm studies with the experimental arm consisting of 2 to 3 cycles of cisplatin and 5-FU and the control arm consisting of total laryngectomy and postoperative RT. Conventionally fractionated RT delivering a total dose of 70 Gy was delivered in CT responders, while nonresponders were treated with total laryngectomy and postoperative RT. The results of combined CT and RT vs. primary surgery and postoperative RT in locally advanced carcinomas of the larynx and hypopharynx achieved in these 3 trials were investigated in a specific analysis as the 3rd metaanalysis in the paper of Pignon et al. [36]. There was a non-significant trend of a 6% lower survival in the group treated with ICT followed with RT, while more than 50% of the surviving patients in this group had their larynx preserved.

Another trial with the primary endpoint being larynx preservation was the RTOG trial 91-11 [44]. In this multi-institutional large trial patients were randomly assigned to one of 3 treatments: ICT (cisplatin plus 5-FU) followed by RT; RT with concurrent administration of cisplatin; or RT alone. Laryngeal preservation, the primary endpoint of this trial, was superior in the CCRT arm compared to both ICT (88 vs. 75% 2-year laryngeal preservation rate; $p=0.005$) and RT alone (88 vs. 70% 2-year laryngeal preservation; $p <0.001$). ICT followed by

RT achieved similar local control rate as did RT alone, but was associated with greater rate of high-grade toxic effects. The rate of LRC was significantly better with the CCRT approach (78 vs. 61% with ICT followed by RT, and 56% with RT alone). There were no significant differences in laryngectomy-free survival and OS between the 3 treatment arms which pointed out that despite the improvement in LRC, CCRT had not provided an improvement in survival over ICT or RT alone.

The recently published American Society of Clinical Oncology (ASCO) guidelines on the larynx preservation approach state that CCRT with further surgery reserved for salvage offers potential for larynx preservation without compromising survival [45]. However, it must be clear that no larynx preservation approach offers survival advantage with respect to total laryngectomy and appropriate adjuvant therapy.

Renewed interest in induction chemotherapy

The adoption of CCRT as a standard of care for patients with locally advanced HNSCC increased locoregional treatment intensity leading to an increased risk of distant metastatic disease. This lack of impact on distant metastases after CCRT, despite an improvement in survival, has been reported from many of the major phase III trials that have tested this approach [27,28,32]. Consequently, the pattern of treatment failure may be shifting from locoregional recurrence to distant metastatic disease, especially in patients with advanced nodal stage [46,47].

Two European studies have shown evidence of a survival benefit with ICT [48,49] (Table 7). Domenge at al. [48] reporting the results from the trial in oropharyngeal cancer conducted by Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) revealed that OS was significantly better (p=0.03) in the ICT group than in the control group. This is the only trial showing an advantage in OS for ICT over locoregional treatment alone for operable and inoperable patients (p=0.03; Table 7). The subset analysis of inoperable patients in the Italian GSTTC study (Gruppo di Studio sui Tumori della Testa) [49], conducted to evaluate the contribution of ICT to the survival in patients with stages III and IV HNSCC suggested that this patients' category benefited from ICT in term of OS (p=0.04; Table 7). The updated results for OS after a minimum follow-up of 10 years were reported by Zorat et al. [50]. The subset analysis showed that among inoperable patients there was a statistically significant better survival observed in the ICT group compared to patients who did not receive ICT (5-year survival: 21 vs. 8%; 10-year survival 16 vs. 6%; p=0.04).

Anticipating that ICT decreases the risk of distant metastases [41,49], and accepting the fact that CCRT is primarily directed to improve locoregional therapy, it seems reasonable to presume that the use of both ICT and CCRT in a sequential manner may provide optimal benefit for patients with locoregionally advanced HNSCC. Two randomized phase III studies using sequential therapy evaluated the benefits of the addition of taxane to platinum plus 5-FU-based ICT [51,52]. The TAX 324 study [51] evaluated induction cisplatin and 5-FU with or without docetaxel followed

Table 7. Phase III trials demonstrating improvement in survival rates with induction chemotherapy

Trial and patient characteristics [Reference]	*Study arm*	*Survival*
Domenge et al. [48] (GETTEC) (n = 318) Stage III/IV disease; oropharynx	Experimental arm: ICT (3 cycles with cisplatin and 5-FU) + LRT (surgery plus RT or RT alone)	Median survival of 5.1 years; OS significantly better (p=0.03)
	Control arm: same LRT without CT	Median survival of 3.3 years
Paccagnella et al. [49] (GSTTC) (n = 237) Stage III/IV disease; oral cavity, oropharynx, hypopharynx and paranasal sinuses	Experimental arm: ICT (4 cycles cisplatin and 5-FU) followed by LRT (surgery plus RT or RT alone)	OS in inoperable patients: at 2 years - 30%, at 3 years - 24%
	Control arm: surgery with postoperative RT in operable patients and RT alone in inoperable patients	OS in inoperable patients: at 2 years - 19%; at 3 years - 10%, (p=0.04)

GETTEC: Groupe d'Etude des Tumeurs de la Tête et du Cou, ICT: induction chemotherapy, 5-FU: 5-fluorouracil, LRT: locoregional treatment, RT: radiotherapy, CT: chemotherapy, OS: overall survival, GSTTC: Gruppo di Studio sui Tumori della Testa e del Collo

by CCRT with weekly carboplatin. There was a highly significant 3-year survival advantage demonstrated in cisplatin/5-FU/docetaxel arm. In the study conducted by the investigators in Madrid [52], ICT treatment of paclitaxel, cisplatin, and 5-FU was compared with standard cisplatin and 5-FU induction therapy, both followed by CCRT with cisplatin. The addition of paclitaxel to standard ICT resulted in a trend for longer OS (p=0.06). The data from both trials are consistent suggesting that a triplet combination including a taxane has potential to emerge as a standard choice for induction chemotherapy in the future [33]. However, so far, no level 1 of evidence data has shown the superiority of ICT followed by CCRT over CCRT [53].

Adjuvant therapy following radical surgery in locally advanced HNSCC

Although no large randomized trial has ever been carried out, the "standard" treatment for patients with locally advanced HNSCC has been radical surgery followed by RT. Despite the addition of adjuvant RT on adequate surgical resection with negative margins, the 5-year survival rate for these patients is usually less than 30% [25]. In the presence of high-risk pathological features being predictors of recurrence and represented by surgical margins microscopically involved, extracapsular extension in positive lymph node, two or more positive lymph nodes, positive lymph nodes at IV and V levels in patients with tumors arising from oropharynx and oral cavity, vascular embolism and perineural infiltration, the addition of adjuvant RT also led to unsatisfactorily high risk of local recurrence (27-61%), distant metastases (18-21%), and death (5-year survival rate 27-34%) [54].

Based on the assumption that surgery may be a trigger of accelerated proliferation of remaining tumor cells, 2 phase III trials conducted to investigate the role of AF in the postoperative setting compared to conventionally fractionated postoperative RT failed to demonstrate any significant improvement of LRC and survival with accelerated postoperative RT [55,56]. In the randomized trial exploring the possible advantage of postoperative-CAIR (p-CAIR) in patients with adverse pathological features, an improvement of LRC was shown only in patients with cancer of oral cavity and oropharynx [21].

Two similar, large-scale, postoperative randomized independent trials designed by the EORTC and RTOG were conducted to evaluate the role of high-dose CCRT in the postoperative treatment of high risk head and neck tumors (Table 8) [57,58]. Both trials evaluated the role of concomitant cisplatin given every 3 weeks (100 mg/m^2 on days 1, 22, 43) during RT (60-66 Gy) . In 2004 NCI level I evidence for recommendation was established because both studies demonstrated that adjuvant CCRT was more efficacious with respect to RT alone in terms of LRC and DFS [24]. Currently, CCRT should be the gold standard for resected patients at high-risk of failure.

Conclusion

The evidence-based treatment in locally advanced HNSCC with respect to RT and CT can be schematically resumed in an evidence-based algorithm (Figure 1). Radical resection and adjuvant therapy is performed in case of resectable tumors, patients' high performance status, and no comorbidities. Resected patients at low risk of failure are treated with adjuvant RT while in presence of high-risk pathological features for locoregional failure, adjuvant CCRT should be carried out. Definitive RT is performed for resectable tumors in an attempt to preserve organ function and in

Table 8. Comparative analysis of treatment outcome in EORTC trial 22931 and RTOG trial 9501

Trial [Reference]	*DFS*	*OS*	*LRFR*
Bernier et al. [57]			
(EORTC 22931)	(5-year estimates)	(5-year estimates)	(5-year estimates)
Experimental arm:	47% (p=0.04)	53% (p=0.02)	17% (p=0.007)
Control arm:	36%	40%	31%
Cooper et al. [58]			
(RTOG 9501)	(2-year estimates)	(2-year estimates)	(2-year estimates)
Experimental arm:	54% (p=0.04)	64% (p=0.19)	18% (p=0.01)
Control arm:	45%	57%	28%

EORTC: European Organization for Research and Treatment of Cancer, DFS: disease-free survival, OS: overall survival, LRFR: locoregional failure rate, RTOG: Radiation Therapy Oncology Group

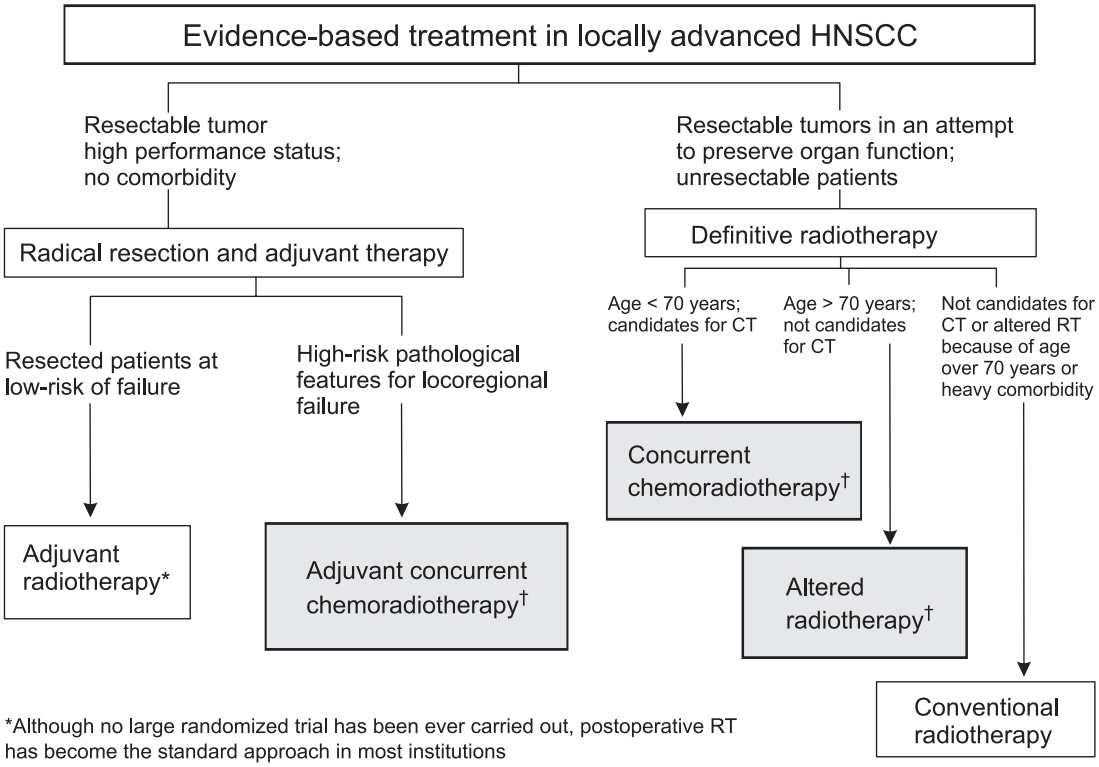

Figure 1. Evidence-based algorithm for radiotherapy and chemotherapy in locally advanced head and neck squamous cell carcinoma.

unresectable patients. CCRT is the treatment of choice for patients with age less than 70 years and when they are candidates for CT. In older patients and in those who are not candidates for CT altered fractionated RT should be considered. Conventional RT should be used only if patients are not candidates for CT or altered RT because of age over 70 years or severe comorbidity.

Nevertheless, advances in tumor biology have created new opportunities to develop specific molecular strategies that selectively increase the tumor response to radiation. Many of these strategies are being tested in preclinical and clinical trials, some of which have already reported encouraging results. The use of CCRT, the appropriate application of the newer CT active agents, and the inclusion of the biological and specific targeted compounds as part of therapy in these patients is expected to provide further improvement in treatment outcomes. A number of interesting strategies are also in preclinical or early clinical development for modifying the induction or processing of radiation injury in normal tissues. Finally, it should be mentioned that patient's preference, physician judgment and toxicity issues must be considered as important factors in determining clinical management for individual treatment approach.

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