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Moderately accelerated intensity-modulated radiation therapy using simultaneous integrated boost: practical reasons or evidence-based choice? A critical appraisal of literature

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Moderately accelerated intensity-modulated radiation therapy using simultaneous integrated boost: practical reasons or evidence-based choice? A critical appraisal of literature

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Running title: SIB-IMRT: practical reasons or evidence-based choice?

Keywords

Head and Neck Cancer; Squamous cell carcinoma; Radiotherapy; Intensity modulated radiotherapy; Simultaneous integrated boost.

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Abstract

Concurrent chemo-radiotherapy is the non-surgical mainstay of treatment for locally advanced head and neck squamous cell carcinoma (HNSCC). The following aspects have emerged as fundamental components of the combined approach: first, intensity modulated radiotherapy (IMRT) is the minimum standard technical requirement, with level 1 evidence in support of its reduction of late treatment-induced morbidity in comparison with 3D conformal radiotherapy. Second, cisplatin – based chemotherapy is the preferred systemic agent to be associated with radiation, with 100 mg/m^2 every 3 weeks deemed as the reference schedule. Because of significant progress in irradiation techniques achieved in last 15 years, the optimal fractionation schedule in modern radiation era remains controversial, especially for locally advanced disease. The purpose of this work was to perform a critical review on the value of moderately accelerated IMRT using simultaneous-integrated boost (SIB) in HNSCC, aiming to provide insights on current clinical practice and directions for future research.

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is a remarkably heterogeneous malignancy and improving survival outcome continues to be a major challenge for clinicians, particularly for patients with locally advanced disease [1]. Today, especially in the USA and Western Europe, a growing number of HNSCC cases is human papilloma virus (HPV)-related, being HPV positivity recognized as a strong prognostic factor [2]. Depending on clinical circumstances, cisplatin-based chemo-radiotherapy (CRT) represents the standard of care, both in primary and adjuvant setting [1]. At present, intensity-modulated radiotherapy (IMRT) is the preferred technique for HNSCC management [1]. Its main advantage over 3-dimensional (3D) conformal radiation therapy (RT) is to confine high dose intensities to target volumes while dropping doses to surrounding organs at risk and thus reducing morbidity. Traditionally, dose per fraction ranges from 1.8 to 2 Gray (Gy) up to a total dose of 50-70 Gy using a sequential boost (SEQ) to the primary or the tumor bed [1]. Simultaneous integrated boost (SIB) has been developed to improve planning efficiency and assure dose escalation to macroscopic disease [3]. SIB-IMRT is a favorable solution mainly because it allows i) different therapeutic dose levels to target volumes with a higher biologically equivalent dose (BED) to the gross tumor with single dose fraction slightly higher than 2 Gy, ii) a single plan with intrinsic tight dose distribution, iii) a shorter overall treatment time (OTT), iv) a concurrent CRT approach, v) a superior dose painting when advanced techniques are available, such as intensity-modulated arc therapy and volumetric modulated arc therapy. However, over the years, several fractionation modifications with or without

concomitant chemotherapy (CHT) have been tested to improve therapeutic ratio and potentially enhance tumor control [3]. Briefly, three types of altered fractionation have been proposed: hyperfractionated (higher total dose with 1.2 Gy/fraction delivered twice daily and same OTT), moderately accelerated (same total dose and shorter OTT) and very accelerated (lower total dose and shorter OTT) [4]. The updated meta-analysis of radiotherapy in squamous cell carcinomas of head and neck (MARCH) defined the crucial role of hyperfractionated RT over other altered fractionation regimens, due to its absolute benefit in overall survival (hazard ratio, HR = 0.83, 95% confidence interval CI 0.74-0.92) with an absolute difference at 5 years of 8.1% (95% CI 3.4-12.8) [5]. However, there is no consensus on what fractionation should be considered standard of care in concurrent CRT. This article provides an insight on current fractionation schedules to potentially suggest a more tailored treatment approach in patients with locally advanced HNSCC. We focused on the available evidence supporting altered fractionation (AF) and SIB-IMRT.

Discussion

Literature search strategy

All the available literature, including abstracts and full text manuscripts, regarding altered fractionation and concomitant CRT strategies in non-metastatic locally advanced HNSCC was reviewed. PubMed search was performed between January 2009 and November 2019 using the following combinations of research criteria: "cancer", "carcinoma", "head and neck", "oral cavity", "oropharyngeal", "oropharynx", "hypopharynx", "larynx", "human papilloma virus", "HPV", "radiotherapy", "IMRT", "altered fractionation", "hyperfractionation", "accelerated fractionation", "SIB" and "toxicity". Only publications in English were retained.

We excluded studies including mostly postoperative cases or nasopharyngeal cancer patients only or those without survival outcomes and/or toxicities analysis and/or details on dose prescription. Reference lists of previously published consensus guidelines, reviews and meta-analyses were explored. Abstract from international meetings (European Society of Medical Oncology, European SocieTy for Radiotherapy & Oncology, American Society for Radiation Oncology and American Society of Clinical Oncology) were included only if with appropriate and sufficiently powered statistical data. For the sake of our analysis, we referred to CRT as the preferred non-operative, curatively-intended strategy. Thus, we did not include induction chemotherapy trials since in the frame of non-nasopharyngeal HNSCC alone its role (followed by RT alone) is supported by level 1 evidence for larynx preservation purpose only. To evaluate the impact of RT schedule in the current IMRT era, we decided to focus primarily on phase III studies in order to support our analysis with the highest level of evidence available. In addition, the largest retrospective series including at least 80 patients using accelerated SIB-IMRT with or without a comparison with conventional sequential IMRT approaches were eligible. Based on these criteria, a total of 31 manuscripts were considered. Details of the main studies reviewed are reported in Table 1 (SIB-IMRT retrospective series) and Table 2 (IMRT randomized trials).

Altered fractionation: the background

A remarkable lesson from published studies over the past 25 years testing altered fractionated regimens for the primary treatment of locally advanced HNSCC has been that both AF and hyperfractionation (HF) have shown therapeutic gains compared to conventional fractionation (CF) with 2 Gy per day to a total of 70 Gy over 7 weeks. In particular, AF reducing OTT by 1 week, either by giving six fractions of 2 Gy per week without total dose changes or by using a concomitant boost (CB) strategy with a 3% increase of the

total dose, allowed a significantly better loco-regional control (LRC) compared to CF (approximately 15% absolute improvement). As expected, acute toxicity increased as well, but the risk of clinically significant late effects did not [6]. Also HF trials using 1.1-1.2 Gy per fraction with a total dose escalation of 7-17% over 6-7 weeks showed a significantly better LRC, with significantly higher acute oral mucositis rates and no detectable increase in late normal-tissue injury compared to CF [6]. The MARCH meta-analysis update, including 34 randomized trials representing 11969 patients with mostly (75%) primary oropharynx or larynx lesions, showed that HF led to a significantly higher overall survival benefit (8.1% at 5 years) over CF than AF without total dose changes, even if slightly different patient populations had been considered in each fractionation group [5]. The clinical superiority of HF has been also emphasized in the Radiation Therapy Oncology Group (RTOG) 9003 study [7]. To date, the RTOG 9003 is the largest randomized trial on pure RT fractionation. Although the cumulative incidences of loco-regional failure were very similar between HF and AF-CB arms, at 5-years HF but not AF improved LRC and OS without increasing long term toxicity over CF [7]. Despite the achievement of identical LRC rates, the reason for HF benefit over AF remains unknown. Within the RTOG, HF did not become the standard or "control" RT fractionation to be used in controlled investigations. Logistic and financial reasons along with early trial results favored AF-CB over HF [7]. Indeed, preliminary clinical data showed the superiority of both AF-CB and HF over CF in terms of LRC without difference in persistent severe late toxicity among fractionation regimens [7]. Thus, several schedules have been investigated in the subsequent RTOG trials to test the best approach with or without CHT. In RTOG 0129 trial, patients with locally advanced HNSCC were randomized to either CF plus concomitant cisplatin (three-weekly 100 mg/m^2 for 3 cycles) or AF-CB with concomitant cisplatin (100 mg/m^2 for 2 cycles) [8]. In the AF group, treatment acceleration was achieved by giving the boost dose as second daily dose in the last 12 treatment days. Therefore, the primary tumor and involved neck nodes were planned to

receive 72 Gy in 42 fractions over 6 weeks reducing OTT by 1 week over CF. However, IMRT was not allowed and radiation technique consisted of 2D/3D conformal RT [8]. Interestingly, there were no significant differences between AF plus two cycles of cisplatin and CF plus three cycles of cisplatin [8]. Based on these results, the RTOG 0522 trial was designed accordingly [9]. IMRT was used and treatment acceleration was achieved by delivering 6 fractions per week for 5 weeks concomitantly to two cycles of cisplatin at usual dosage [9]. The OTT reduction strategy was similar to that investigated in the Danish Head and Neck Cancer Group (DAHANCA) 6 and 7 trials: one fraction daily, from Monday to Friday, and the sixth fraction given on Saturday or Sunday, or as an extra fraction on a weekday, with at least six-hour interval between consecutive fractions. In addition to different tumor sites – glottic larynx in DAHANCA 6 and supraglottic larynx, pharynx and oral cavity tumors in DAHANCA 7 –, the main difference between the two DAHANCA trials was that the DAHANCA 6 dealt only with the fractionation effect, whereas the DAHANCA 7 included treatment with the hypoxic radiosensitiser nimorazole [10]. Compared to CF, the six-fractions-weekly regimen assured a significant control benefit on primary tumor (76% versus 64%) but did not improve regional control [10]. The general benefit of this AF strategy has been confirmed in the International Atomic Energy Agency (IAEA) ACC trial, concluding that it could be effectively applied in developing countries, where few therapeutic resources are available, potentially being a new international standard of treatment [11]. Over the years, accelerated regimen of six fractions of RT per week has become a standard option in the United States as well as a common fraction regimen in the RTOG investigations [1]. For instance, in the recently published NRG Oncology RTOG 1016 trial, patients with locally advanced HPV-positive oropharyngeal carcinoma received accelerated IMRT delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 hours apart) and were randomly assigned to receive either concomitant cetuximab or cisplatin [12].

It should be acknowledged that in the accelerated IMRT era reducing OTT by 1 week according to the DAHANCA andRTOG trials is more convenient and less expensive than AF-CB or HF RT. However, at present, based on the MARCH-HPV project results, the RT fractionation regimen cannot be solely based on HPV status because its expression had no predictive impact on response to AF [13].

Simultaneous integrated boost: what's the evidence?

SIB-IMRT is a dose painting strategy that assures dosimetric and safety advantages over SEQ-IMRT plans [14]. It allows to implement a dose-escalation approach using fraction size (FS) higher (> 2.0 Gy per fraction – hypofractionation) than the conventional 2 Gy per fraction. Assuring OTT reduction and same total dose over CF, SIB-IMRT represents an option to achieve acceleration but without changing the number of weekly fractions. Its main limit is the intensity of normal tissue toxicity, both in acute and late phases (as consequence of acceleration itself). The increase in single fraction dose reduces the therapeutic gain, since the FS is the main factor determining late effect and influencing early responder tissues [15, 16]. It is axiomatic that with dose escalation there should be limitation to the irradiated volume. This is certainly true for 2D/3D conformal RT. Actually, due to the strict "conformal avoidance" of critical structures achievable with SIB-IMRT, the delivery of high FS to high risk volume in a shortened OTT should be hazardous only for normal tissues embedded in this volume [17]. Mohan suggested an unacceptable toxicity in case of fraction number lower than 30 and total dose escalation over 70 Gy [14]. In these conditions it could be prohibitive to add concomitant CHT. In the last few years, a variety of accelerated hypofractionated SIB-IMRT regimens have been employed worldwide, without the possibility to define a standard. Main retrospective series are listed in Table 1. On the whole, a marked heterogeneity in terms of number of patients, primary tumor site, disease stage, RT setting,

concomitant systemic approach and study design makes any comparison difficult. Similarly, a plethora of IMRT fractionation regimes (12 fractionation schedules over 14 cancer centers around the world) in HNSCC has been described by Ho et al [18]. The vast majority of centers employed an accelerated fractionation. Among these schedules, the modestly hypofractionated regimen (≤ 2.2 Gy per fraction, with an OTT ranging from 6 to 6.5 weeks) and the dose escalated hypofractionated schedule (> 2.3 Gy per fraction, with higher total dose and OTT of 5 to 6.5 weeks) were most commonly used (in 2 and 4 centers, respectively) on top of concomitant platinum-based CHT [18]. In several large retrospective series, dose per fraction to high risk target volume was increased up to 2.2 Gy per fraction for a total dose of 66-69.96 Gy in 30-33 fractions [19-24]. This altered fractionation schedule was usually associated with concomitant CHT. Median follow-up ranged from 17 and 37 months. Overall, local control and survival outcome were excellent, with percentage (at a minimum 2-year time point) in the range of 80-90% and 80%, respectively. Even though in the reports by Studer [22] and Daly [24] the type and frequency of acute and late effects referred to both definitive and postoperative cases, severe acute mucositis and dysphagia occurred in 15-50% of patients in the remaining series whereas late severe toxicities were reported with a very low frequency. To put the results of largest retrospective SIB series into perspectives, fractionation regimens and outcome results from phase III randomized trials are reported in table 2 [9, 12, 25-29]. Moderately accelerated RT in 6 weeks with concomitant cisplatin- based CHT was the reference arm in the majority of studies, regardless the primary endpoint of trial. Two trials were designed with a different "standard treatment" regarding concomitant CHT. In particular GORTEC 2007-01 trial [27] was designed to investigate the effect of adding concurrent cetuximab to a carboplatin-5 fluorouracil backbone and RT (given as conventionally fractionated IMRT with sequential approach) compared with bio-radiotherapy in locally advanced HNSCC. The PARSPORT trial was designed to assess parotid-sparing IMRT compared with conventional RT [28]. In

the IMRT group, a SIB-IMRT was prescribed. Namely, primary tumor and involved lymph nodes were treated with 65 Gy in 30 fractions (2.16 Gy per fraction, 5 days per week) and nodal levels received 54 Gy in 30 fractions (1.8 Gy per fraction, 5 days per week). No concurrent CHT was administered, but patients who had received induction CHT were eligible. Both radiation-induced xerostomia and global quality of life scores were significantly better in patients treated with SIB-IMRT compared with conventional RT, whereas there were no differences in terms of LRC and OS rates between groups. Recently, two phase 3 trials, the De-ESCALaTE [29] and RTOG 1016 [12] investigated the role of a de-intensification approach in HPV-positive oropharyngeal cancer testing cetuximab in place of cisplatin concurrently with RT. Interestingly, RT was delivered with CF in the De-ESCALaTE study and with acceleration in six weeks in the RTO G1016 trial. Both studies failed in demonstrating that bio-radiotherapy was associated with non-inferior survival and comparable toxicity profile compared with cisplatin-based CRT.

Overall, the safety and tolerability of SIB as a dose-painting strategy was tested in a small number of prospective phase 1/2 trials, with or without concomitant or neoadjuvant CHT [30, 31]. Lauve et al [30] demonstrated that a total dose of 70.8 Gy in 30 fractions of 2.36 Gy can be safely delivered as the sole treatment in HNSCC. This SIB-IMRT regimen defined the maximum tolerated dose. Higher daily dose per fraction (2.46 Gy) resulted in uncontrolled severe toxicity onset resulting in prolonged RT break [30]. On the other hand, Leclerc at al described the feasibility of dose escalation up to 75 Gy in 30 fractions of 2.5 Gy using SIB-IMRT without concomitant CHT in early and moderately advanced (T2 N0-1 and T3 N0) HNSCC cases [31]. Data from SIB-IMRT with concomitant CHT studies with three different doses per fraction (2.25 Gy to a total dose of 63 Gy in 28 fractions; 2.4 Gy to a total dose of 67.2 Gy in 28 fractions; 2.17 Gy to a total dose of 65 Gy in 30 fractions) have been described in literature [32]. These studies demonstrated that incidence, peak prevalence and recovery from severe dysphagia and oral mucositis were significantly higher in patients receiving 2.4

Gy per fraction [32]. Final long term results revealed high 5-year LRC, PFS, and organ preservation rates, with acceptable late toxicity (6.4% of cases developed late severe dysphagia) [33]. Another strategy to improve loco-regional control minimizing late normal tissue toxicity was performed using SIB-IMRT with concurrent cetuximab [34]. Patients with stage II-III disease (T2-3 N0; T1-3 N1) were treated with 62.5 Gy in 25 daily fractions over 5 weeks. This treatment modality was effective on tumor control with an acceptable acute toxicity, low rate of late toxicity and marginal impact on quality of life [34]. It is pivotal to underline that in this trial, the extension of the high risk and low risk volumes are smaller than those usually defined in locally advanced disease including T4, N2 and N3 stages. Thus, a marked acceleration in 5 weeks without an increase in total dose was shown to be tolerable for this distinct category.

To summarize, the consistency of all these results confirms the safety and the feasibility of a hypofractionated accelerated SIB-IMRT concomitant to CHT or cetuximab with a total dose equal or slightly inferior to 70 Gy in 30 to 33 fractions in the majority of cases.

Based on these assumptions, a main question remains:

What accelerated fractionation should be considered standard of care in concomitant CRT approach?

Based on 87 randomized trials representing 17,346 patients, the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) clearly established an absolute OS benefit of 4.5% at 5 years for chemotherapy and a more pronounced benefit of the concomitant CRT as compared to sequential approaches [35]. While the superiority of AF and SIB-IMRT over FC has been proven, the optimal accelerated fractionation to be used remains to be firmly established. A recent meta-analysis compared treatment outcomes of conventionally fractionated CRT versus AF alone [36]. In total, 5 randomized trials (1117 patients) were included in the final analysis [37-41]. Despite different patient and treatment

characteristics, all these studies directly randomized patients to conventionally fractionated CRT or an accelerated regimen arm. One trial used a split-course AF schedule – 1.6 Gy per fraction, 2 fractions daily, 5 days/week for a dose of 64-67.2 Gy with planned 2 week treatment gap after 2.5 weeks – [37]; two trials used two different forms of acceleration, including very accelerated (1.8 Gy per fraction, 2 fractions daily, 5 days/week for a total dose of 64.8 Gy in 36 fractions in 3.5 weeks) and accelerated regimen s(2 Gy per fraction, 6 days/week for 66-70 Gy) [38, 39]; the others used a CB regimen boosting primary tumor and positive nodes at 1.2 Gy/ fraction given 6-8 hours apart during last 2 weeks of RT or 1.5 Gy/fraction given 6 hours apart during last 3 weeks [40, 41]. Overall, the results provided moderate (for OS and disease-free survival) and low (for LRC) quality evidence mainly due to small sample size and severe indirectness of included studies [36]. In fact, three trials used carboplatin with 5-fluorouracil and one weekly cisplatin, respectively [37-40]. Only one trial used the standard three-weekly cisplatin-based CHT [41]. In addition, HF RT was not performed in any of them, despite its proven efficacy compared to conventional RT [4].

The combination of CHT and HF RT has been examined in a subsequent meta-analysis, including six trials and 1280 patients [42]. Results supported the role of concurrent CHT and HF RT. Compared to HF alone, concomitant treatment showed improvement in OS (HR 0.77, CI 95% 0.66-0.89), cancer-specific survival (HR 0.72, CI 95% 0.60-0.88), progression-free survival (HR 0.74, CI 95% 0.63-0.87) and LRC (HR 0.64, CI 95% 0.55-0.75) without a significant increase in severe acute and late toxicities. However, it should be noticed that in individual studies, concomitant CHT schedules, as well as RT techniques, were not the standard of care in daily HNSCC practice. No firm conclusions can be drawn but probably it is possible to speculate that direct comparisons of HF versus CF, both with concomitant CHT, might result in clinical benefit. At present, this assumption is supported by a mixed treatment comparison meta-analysis showing that CRT using moderate HF and platinum-based concurrent CHT leads to the highest probability of survival, compared with other

treatment modalities [43]. Moreover, a notable finding is that acceleration might compensate the absence of a third cycle of concomitant CHT [9, 38]. According to the MACH-NC meta-analysis, concomitant platin-based CHT is associated to the maximum survival benefit [35]. But benefit of concomitant CHT appears to be dissimilar depending on its cumulative dose. At present the recommend dose is cisplatin 100 mg/m^2, three times during RT, up to a cumulative dose of 300 mg/m^2 [1]. However, in routine practice, a substantial fraction of patients do not receive the third planned cycle due to severe toxicity, primarily mucositis. Establishing the minimal cumulative dose able to guarantee a beneficial antitumor effect while reducing toxicity could be an important clinical issue.

The relevant literature on survival results after RT alone and concurrent cisplatin-based CRT indicated a significant positive correlation between OS improvement and higher cumulative cisplatin dose, even though an effective benefit beyond the cumulative cisplatin dose of 200 mg/m^2 is confounded [44]. A pooled analysis of 404 HPV-positive and 255 HPV-negative HNSCC patients demonstrated a survival benefit of cumulative dose > 200 mg/m^2 in HPV-negative cases, but not in HPV-positive cohort, although T4 or N3 disease may benefit from a higher cisplatin dose [45].

Conclusion

Robust literature data have consistently demonstrated that treatment intensification, either by concomitant CHT or altering the fractionation, improves survival outcomes in locally advanced HNSCC. However, there are no direct comparative studies to propose definitive conclusions. Therefore, how do these literature data fit in routine clinical practice? SIB-IMRT is largely used but actually no high-quality evidence is available on its safety and efficacy compared to recommended standard cisplatin-based CRT using conventional fractionation. SIB-IMRT is mainly dictated by logistic issues, such as machine slots and patient

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convenience. The BED of SIB-IMRT is slightly higher than that of conventional fractions, but at present the optimal dose prescription is doubtful.

However, it remains i) to established whether AF jeopardizes treatment compliance and negatively affects toxicity profile and quality of life; ii) to evaluate radiobiological comparison between fractionation schemes in IMRT era; iii) to clarify whether HPV-positive and HPV-negative disease, despite their different radiosensitivity [46], benefit from the same SIB fractionation; iv) to test whether different systemic agents can be associated with AF RT to confer additional survival benefit minimizing morbidity. Hopefully, future clinical trials will be designed to vigorously pursue definitive recommendations.

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Captions and legends

table 1: **SIB-IMRT main retrospective series.**

IMRT: intensity modulated radiotherapy; 2D: two dimensional; 3D: three- dimensional; RT: radiotherapy; SEQ: sequential; SIB; Simultaneous integrated boost; BID: bifractionation; fr: fraction; OTT: overall treatment time; FU: follow-up; Gy: Gray; PFS: progression-free survival; y: year; vs: versus; LC: local control; RC: regional control; LRC: locoregional control; CRT: conventional chemoradiotherapy; HPV: human papilloma virus; LC: local control; DFS: disease-free survival; OS: overall survival; mo: months; y: years, NA: not available vailable; CHT:chemotherapy

table 2: randomized phase 3 trials.

IMRT: intensity modulated radiotherapy; fr: fraction; OTT: overall treatment time; FU: follow-up; RCT: randomized clinical trial; CHT:chemotherapy; cetux: cetuximab; RT: radiotherapy; Gy: Gray; PFS: progression-free survival; y: year; vs: versus; LRC: loco-regional control; HPV: human papilloma virus; NIM: nimorazole; SIB: simultaneous integrated boost; LRF: loco-regional failure; OS: overall survival; 2D: two dimensional; 3D: three dimensional; G: grade ; AUC: area under the curve; NA: not available

Table 1

	Trial	Patients													
Author	Study period	Population	Total treatment	Concurrent systemic therapy	RT technique	Dose/fr to High-Risk target (Gy)	OTT	High-risk target (Gy)	Intermediate-risk target (Gy)	Low-risk target (Gy)	Median FU	LC%	RC%	DFS%	OS%	Consideration
Spiotto_2014 [19]	1993-2012	stage III-IVB oral cavity, oropharynx, hypopharynx, larynx, nasopharynx	379	Cisplatin (146) Carboplatin (52) 5-fluorouracil - hydroxyurea paclitaxel (137) Other (44)	3D-RT (125)	2 1 daily fr or 1.2-.1.5 2 daily frs (5 days/w)	NA	74 Median dose	52 Median dose	39.5 Median dose	25.8 mo 17.5 mo	75.7 (2y) 70.3 (2y)	84.5 (2y) 86.9 (2y)	59 (2y) 0.4 (2y)	70.2 (2y) 71.1 (2y)	25% of patients received RT t in postoperative setting; induction CHT was given to39.3% of pts. Compared to 3D-RT and IMRT-SEQ moderately IMRT-SIB provided similar outcomes and potentially less toxicity.
					IMRT- SEQ(120)	2 1 daily fr or 1.2-.1.5 2 daily frs (5 days/w)	NA	71.25 Median dose	51 Median dose	50 Median dose						
					IMRT-SIB (134)	2..2 2.12 1 daily fr (5 days/w)	30 frs 33frs	66 69.96	60 59.4	54 54.12	16.3 mo	66.7 (2y)	76.8 (2y)	54.5 (2y)	66.9 (2y)	
Vlacich_2017 [20]	2003- 2012	stage III-IVB orpharynx hypopharynx, larynx, oral cavity, paranasal sinus, unkown primary, nasopharynx	209	97.5% of pts received carboplatin/paclitaxel	IMRT- SEQ(68)	2.1	33 frs (5 frs/w)	69.3	NA	50.4	30.6 mo	88.2 (4y)	92.1 (4y)	63 (4y)	69.3 (4y)	Induction CHT in 78% of pts No differences in outcomes between the two treatment delivery approaches. A higher rate of grade 3 and 4 radiation dermatitis and dysphagia were observed in the SIB group, however this did not translate into differences in late toxicity.
					IMRT-SIB (141)	2.1	33 frs (5 frs/w)	69.3	NA	56.1	56.8 mo	85.9 (4y)	91.6 (4y)	69 (4y)	76.8 (4y)	
Kuo YH_2019 [21]	2011-2015	Stage III-IV Ooropharynx, hypopharynx	200	100% of pts received drug(s) not specified	IMRT- SEQ(100)	2	35 frs (5 frs/w)	NA	NA	44-50	33 mo	NA	NA	NA	47 (5y)	43.5% of patients received induction and/or adjuvant CHT No differences in OS

Study	Years	Stage / Site	N	Chemotherapy	Technique	Dose/fx	Fractions	Dose 1	Dose 2	Dose 3	Follow-up	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Comments
					IMRT-SIB (100)	2	35 frs (5 frs/w)	NA	NA	54-63		NA	NA	NA	54 (5y)	No HPV status data available
Studer G_2010 [22]	2002- 2008	Stage II-IVB Larynx, Hypopharynx	123	85% of pts received concomitant cisplatin or cetuximab	IMRT-SIB	2.2	30 (5 frs/w)	66	NA	54	26 mo	82% (2y)	90% (2y)	75% (2y)	83% (2y)	Pts with substantial parts of the pharynx or more than half of the larynx involved in the boost volume were given 2.0 Gy per session to 70 Gy, with 5 to 6 fractions per week (n = 44, 36%).
						2.1	33 (5 frs/w)	69.6	NA	54						
Clavel S 2012 [23]	2000 - 2007	stage III-IVB Oropharynx	100 / 149	100% of patients received concomitant carboplatin and 5-fluorouracil	IMRT-SIB +CT	2.12	33	69.96	59.4	50.4	42 mo	95.1 LRC (3y)		84.4 (3y)	85.3 (3y)	SIB- was associated with statistically favorable LRC and survival rates, with less xerostomia and acute dermatitis compared with CRT .
					Conventional CRT	2	35	70	60	50		69.3 (3y)		92 (3y)	75.2 (3y)	No HPV status data available
												p= 0.005		p= 0.001	p< 0.001	
Daly ME_ 2010 [24]	2001- 2007	Stage II-IV Oropharynx	85 definitive 22 (postperative)	87% of pts received concomitant cisplatin, carboplatin or cetuximab- based CHT	IMRT-SIB	2.2	30	66 (definitive)	54 (definitive)	52 (definitive)	29 mo	92 LRC (3y)		83 (3y)	81 (3y)	-

Table 2.

Author	Acronym	Type	Enrollment time	Population	Total	Treatment	Concurrent systemic therapy	IMRT	Technique	Total dose	Dose fr	OTT	Definitive planning dose	High-risk target	Low-risk target	Median FU	Primary end point	Outcomes	Consideration
Ang_2014 [9]	RTOG 0522	Phase III RCT	Nov 2005 - May 2009	stage III-IV oropharynx, hypopharynx, larynx	891	CHT-RT (447) vs CHT-cetux-RT (444)	Cisplatin 100 mg/m2 (on days 1 and 22) +/- weekly cetux 250 mg/m2 (400 mg/m2, loading dose)	771	NA	70 Gy	2 Gy	6 weeks	NA	NA	NA	3.8 years	PFS	Similar 3-y PFS (61.2% vs 58.9%), 3-y OS (72.9% vs 75.8%), 3-y LRF (19.9% vs 25.9%), 3-y DM (13% vs 9,7%)	419 (93.7%)and 402 (90.5%) patients received 2 cycles of cisplatin
Gillison_2018 [12]	RTOG 1016	Phase III RCT	Jun 2011 - Jul 2014	HPVpositive oropharyngeal carcinoma (T1-2 N2a-3 or T3-4 N0-3)	849	cetux-RT (425) vs CHT-RT (424)	cetux 250 mg/m2 (400 mg/m2, loading dose) or Cisplatin 100 mg/m2 (on days 1 and 22)	849	NA	70 Gy	2 Gy	6 weeks	NA	NA	NA	4.5 years	OS	lower 5-y OS (77.9% vs 84.6%), lower 5-y PFS (67.3% vs 78.4%), higher 5-y LRF (17.3% vs 9.9%); similar acute (77.4% vs 81.7%) and late (16.5% vs 20.4%) severe toxicity	377 (93%) patients received 2 cycles of cisplatin
Metwally_2015 [25]	IAEA-HypoX	Phase III RCT	Mar 2012 - May 2014	stage I-IV oral cavity, oropharynx, hypopharynx, larynx (except I-II larynx)	82	NIM-RT (39) vs RT (43)	NIM H61.2 g / m2 body surface area	25 (12 + 13)	SIB	66-70 Gy	2 Gy	6 weeks	66-70 Gy (2 Gy/fr)	60 Gy (1.7-1.8 Gy/fr)	50 (1.4-1.5 Gy/fr)	19 months	LRF	Similar 2-y LRF (52% vs 56%) and 2-y OS (51% vs 29%)	Most patients (n = 56) received 2D RT
Mehanna_2016 [26]	PET-NECK	Phase III RCT	Oct 2007 - Aug 2012	stage N2-3 nodal oropharynx, hypopharynx, larynx, oral cavity, occult	564	CHT-RT	at least two doses of concomitant three/four weekly cisplatin 75-100mg/m2 or carboplatin 4.5-5 AUC or weekly cetux 250 mg/m2 (400 mg/m2, loading dose)	332	SIB; sequential	65 Gy; 70 Gy	2.16 Gy; 2 Gy	6 weeks; 7 weeks	NA	NA	NA	36 months	OS	2-y OS 83.2%	
Tao_2018 [27]	GORTEC 2007-01	Phase III RCT	Jan 2008 - Mar 2014	stage III-IV (N0-2b) oral cavity, oropharynx, hypopharynx, larynx	406	CHT-cetux-RT (204) vs cetux-RT (202)	weekly cetux 250 mg/m2 (400 mg/m2, loading dose) +/- 3 cycles of carboplatin 70 mg/m2 on days 1 to 4 and FU 600 mg/m2 on days 1 to 4	164 (80 + 84)	Sequential	70 Gy	2 Gy	7 weeks	70 Gy (2 Gy/fr)	.	50 Gy (2 Gy/fr)	4.4 years	PFS	CHT-cetux-RT higher 3-y PFS (52.3% vs 40.5%), lower LCF (21.6% vs 38.8%), higher severe mucosistis (73% vs 61%) and hospitalizations (42% vs 22%)	
Nutting_2011 [28]	PARSPORT	Phase III RCT	Jan 2003 - Dec 2007	oropharynx, hypopharynx (T1-4, N0-3)	94	3D-RT (47) vs IMRT (47)	None	47	SIB	65 Gy	2.16 Gy	6 weeks	65 Gy (2.16 Gy/fr)	.	54 (1.8 Gy/fr)	44 months	xerostomia ≥ G2	Lower 1-y xerostomia (38% vs 74%), lower 2-y xerostomia (29% vs 83%), similar 2-y PFS (78% vs 80%) and similar 2-y OS (78% vs 76%)	
Mehanna_2018 [29]	De-ESCALaTE HPV	Phase III RCT	Nov 2012 - Oct 2016	HPV-positive low-risk oropharyngeal cancer (T3-4N0, and T1N1-T4N3)	334	CHT-RT (166) vs cetux-RT (168)	cisplatin 100 mg/m2 (on days 1, 22, and 43) or weekly cetux 250 mg/m2 (400 mg/m2, loading dose)	332	Sequential	70 Gy	2 Gy	7 weeks	NA	NA	NA	25.9 months	overall acute and late severe toxicity	Similar severe toxicity, higher 2-y OS (97.5% vs 89.4%) and lower 2-y LRC (6% vs 16.1%)	62 (38%) patients received 3 cycles of cisplatin, 83 (51%) received 2 cycles, and 16 (10%) received 1 cycle