Helical Tomotherapy in Head and Neck Cancer: A European Single-Center Experience

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Head and neck cancer • Helical tomotherapy • Retrospective analysis • Systemic therapy

ABSTRACT

Background. We report on a retrospective analysis of 147 patients with early and locoregionally advanced squamous cell head and neck cancer (SCCHN) treated with helical tomotherapy (HT).

Patients and Methods. Included were patients with SCCHN of the oral cavity (OC), oropharynx (OP), hypopharynx (HP), or larynx (L) consecutively treated in one radiotherapy center in 2008 and 2009. The prescribed HT dose was 60–66 Gy in the postoperative setting (group A) and 66–70 Gy when given as primary treatment (group B). HT was given alone, concurrent with systemic therapy (ST), that is, chemotherapy, biotherapy, or both, and with or without induction therapy (IT). Acute and late toxicities are reported using standard criteria; locoregional failure/progression (LRF), distant metastases (DM), and second primary tumors (SPT) were documented, and event-free survival (EFS) and overall survival (OS) were calculated from the start of HT.

Results. Group A patients received HT alone in 22 cases and HT + ST in 20 cases; group B patients received HT alone in 17 cases and HT + ST in 88 cases. Severe (grade ≥ 3) acute mucosal toxicity and swallowing problems increased with more additional ST. After a median follow-up of 44 months, grade ≥ 2 late toxicity after HT + ST was approximately twice that of HT alone for skin, subcutis, pharynx, and larynx. Forty percent had grade ≥ 2 late xerostomia, and 29% had mucosal toxicity. At 3 years, LRF/DM/SPT occurred in 7%/7%/17% and 25%/13%/5% in groups A and B, respectively, leading to a 3-year EFS/OS of 64%/74% and 56%/63% in groups A and B, respectively.

Conclusion. The use of HT alone or in combination with ST is feasible and promising and has a low late fatality rate. However, late toxicity is nearly twice as high when ST is added to HT. *The Oncologist* 2015;20:279–290

Implications for Practice: This article reports on a European single-center clinical experience with helical tomotherapy (HT) in the treatment of head and neck cancer. It tries to give a realistic reflection of the role of HT in daily practice for patients who are candidates for radiotherapy, either as a primary treatment or in the postoperative setting and either alone or combined with systemic therapy (ST). The use of HT alone or in combination with ST is feasible, with a low late fatality rate. However, late toxicity is substantially higher when ST is added to HT. It seems therefore advisable that patients receiving such combined modality treatments are treated in specialized centers.

INTRODUCTION

In an attempt to improve the outcome of patients with squamous cell head and neck cancer (SCCHN), the use of chemotherapy concurrently with radiotherapy (RT) and RT intensification were implemented widely in the late 1990s and early 2000s [1–6]. However, the toxicity with these approaches is a serious limitation that precludes further treatment intensification and thereby further improvement in outcome [7]. In order to reduce the

toxicity of the classical two- and three-dimensional conformal RT, RT techniques evolved rapidly since the nineties with the introduction of intensity-modulated radiotherapy (IMRT) in different forms [8, 9]. With respect to head and neck cancer, the actual wide use of IMRT in this disease is based on level I evidence of static beam IMRT reducing xerostomia compared with conventional and conformal radiotherapy [10–14]. Therefore,

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IMRT is now considered the standard of care when treating head and neck cancer patients with RT. Evidence of superiority of IMRT in terms of outcome is growing [14, 15]. However, it is unclear whether this outcome benefit of IMRT is due to better targeting of specific regions of concern for tumor control or to the fact that IMRT allows for further treatment intensification, whether by the addition of chemotherapy or biotherapy or by very precise RT dose escalation [16–19].

Rotational IMRT techniques have followed the static beam IMRT and helical tomotherapy (HT) (Accuray, Sunnyvale, CA, <http://www accuray.com>) in particular is an IMRT-dedicated system with an integrated computed tomography (CT) scanner allowing for volumetric image guided radiotherapy. However, besides the fact that the rotational IMRT techniques are clearly faster, there is no evidence from randomized trials that they are superior to any of the static beam techniques [20]. Moreover, there is no clinical evidence of one rotational technique being superior over the other.

The few articles that have been published about the clinical results of HT in head and neck cancer all show excellent short-term (maximum 2 years) results. However, all these studies are small single-center studies [21]. In this article, we review the feasibility, toxicity, and outcome of 147 SCCHN patients treated at our HT facility in 2008 and 2009.

MATERIALS AND METHODS

Patients

All patients had newly diagnosed early or locoregionally advanced SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx [22]. Patients had been treated with surgery before referral (group A) or were to be treated with definitive HT within the context of a nonsurgical approach (group B). HT was given either as a single modality or combined with systemic treatment (concurrently only or concurrently preceded by induction therapy [IT]), the selection of which was based on standard risk-based management or trial participation.

The pretreatment evaluation included a complete history and physical examination, pan-endoscopy, chest x-ray, complete blood count, routine blood chemistry, and CT scan and magnetic resonance imaging (MRI) of the head and neck region. Almost all patients also got a positron emission tomography (PET) scan in search of distant metastasis and as an aid in contouring the primary tumor and suspicious lymph nodes [23, 24].

Treatment Planning and Delivery

For each patient, a contrast-enhanced CT scan with 3-mm slice thickness was made in the treatment position with a customized immobilization mask.

Volumes

The gross tumor volume, the clinical target volume (CTV), and the nearby organs at risk (OARs) were delineated on the Pinnacle system version 7.6 (Philips Medical Systems, Eindhoven, The Netherlands, <http://www.medical.philips.com>). OARs routinely contoured were the spinal cord, brainstem, brain, parotid glands, larynx, mucosa of the mouth, soft palate, base of the tongue, and the constrictor muscles. Lymph node levels were delineated according to the Danish Head and Neck Cancer Group, European Organization for Research and Treatment of

Cancer (EORTC), Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC), National Cancer Institute of Canada (NCIC), and Radiation Therapy Oncology Group (RTOG) consensus guidelines as described by Grégoire et al. [25, 26].

The planning target volume (PTV) was defined as the CTV plus a 3-mm margin, calculated on a cohort of head and neck cancer patients treated with daily megavolt CT image guidance [27]. A planning risk volume (PRV) was created 3 mm around the spinal cord and the brainstem.

Neck Region

Most patients had bilateral neck node irradiation. Lymph node regions were irradiated unilaterally in case of tumors of the oral cavity or oropharynx located at ≥ 2 cm from the midline. The boost volume contained the invaded lymph node level, as well as the neighboring levels and often also the high risk parts of the node negative neck. No lymph node irradiation was done after a neck dissection without lymph node involvement.

Irradiation Techniques

HT plans were made with the treatment planning module for the HT HiArt system version 3.1. The dose to the PTV was prescribed according to the International Commission on Radiation Units and Measurements report 62 [28]. A biological equivalent dose (BED) of 50 Gy in 25 fractions was prescribed to the noninvolved lymph node levels, that is, 50 Gy in 25 fractions in a sequential protocol or 54 Gy in 30 fractions and 56 Gy in 32 or 33 fractions via a simultaneous integrated boost technique. Four patients of group B were included in a dose de-escalation study and received only 49 Gy in 32 fractions (BED of 40 Gy) to the elective lymph node levels [29]. The PTV of the tumor and of the high risk lymph node levels was planned to be 60–66 Gy in 6–6.5 weeks in group A and to be 70 Gy in 7 weeks in patients in group B, all in fractions of 2 Gy. As of May 2008, we started to treat some of the group B patients with a simultaneous integrated boost technique to 69.12 Gy (2.16 Gy/fraction) to the PTV therapeutic, in 32 fractions over 6.4 weeks.

The dose to the PRV of the spinal cord was limited to 50 Gy and a maximum of 59 Gy with 50% of the volume (D50) under 55 Gy accepted to the PRV of the brainstem. The dose to the OARs, including the spinal cord and the brainstem, was kept as low as possible respecting the prescription to the PTV. The reference dose constraints have been reported in a preliminary planning study [30].

All plans were calculated for a beam width of 2.5 cm, with a pitch of 0.287 and a maximal modulation factor of 2.8. All patients were planned to be treated on 5 consecutive days per week.

Quality Assurance

For every patient, an initial dosimetric verification was performed by measurements with ion chambers and film of the individual plan in a phantom geometry. Because no international accepted quality assurance (QA) protocol on HT was available, routine QA was based on recommendations from the company in combination with recommendations from publications [31–33]. International QA guidelines were implemented to the specific situation of HT, as described by us earlier [34]. Verification of patient positioning was done by daily megavolt CT scan followed by an online correction before the start of the actual treatment fraction.

Follow-up and Assessment

During radiotherapy, patients were seen weekly. Acute radiation toxicity was graded according to the RTOG and the EORTC toxicity criteria [35].

After the completion of their treatment, patients were seen every month during the first year, every 2 months in the second year, and every 3–6 months thereafter. Late toxicity (>6 months after HT) was mostly scored by the same radiation oncologist (D.V.d.W.) according to the RTOG/EORTC Late Radiation Morbidity Scoring Schema [35].

A first post-treatment clinical/radiological evaluation was usually obtained 3 months after the completion of radiotherapy; PET-CT scanning was performed in patients with stage ≥ 2 regional lymph node disease of group B. Thereafter, regular (PET-)CT and/or MRI studies were obtained every year in group B patients or earlier on indication in both groups. Thyroid function was tested after extended neck irradiation. Video laryngoscopy was performed routinely, and all patients got a chest x-ray yearly.

Statistical Analysis

Differences in grade 3 and 4 toxicities between different therapies are assessed by chi-square tests. When numbers are small, Fisher exact test is used. Numbers and percentages are reported. Weight loss is compared between therapies with a Mann-Whitney *U* test.

Locoregional failure/progression (LRF), distant failure (DF), and second primary tumor (SPT) rates were assessed by the cumulative incidence method with death of any cause as a competing risk [36]. Event-free survival (EFS) and overall survival (OS) were estimated by the Kaplan-Meier method [37]. All time-to-event endpoints were analyzed for all patients and separately for patients in groups A and B (and in addition also separately for stage III–IV patients of group B) and measured from the start of HT. Failure for EFS was defined as LRF, distant metastases, or second primary or death of any cause. OS was calculated from the start of HT until death from any cause.

In addition, predictors (gender, age, general performance status [World Health Organization], smoking, tumor site, stage, grade, surgery, induction chemotherapy, concomitant chemotherapy, and radiation treatment time [RTT]) for overall survival were studied using Cox regression models. First a simple Cox model was fitted for each covariate, and covariates with *p* values of <0.15 were then entered in the multiple Cox regression model. *p* values below 0.05 were considered significant. All statistical analyses were performed in R 3.0.1 (R Core Team 2013).

RESULTS

Details on the 147 patients treated at the radiotherapy department of the University Radiotherapy Antwerp Unit between January 2008 and December 2009 are given in Table 1. The application of additional therapies to helical tomotherapy subdivided for group A and B is described in Table 2.

IT was given to 48 patients, of whom 36 received solely cytotoxic chemotherapy, that is, the European TPF regimen (docetaxel, cisplatin, and 5-fluorouracil [16]) in 31, weekly carboplatin-paclitaxel in 4, and carboplatin + 5-fluorouracil in 1; 1 patient received induction biotherapy, and 11 had a combination of TPF with biotherapy (cetuximab in 8,

panitumumab in 2, and lapatinib in 1). Complete responses to IT were only observed with the TPF-based regimens (15 of 42; 36%). Of the 108 patients that received chemotherapy and/or biotherapy concurrently with HT, 30 received low-dose weekly cisplatin, 7 received high-dose 3-weekly cisplatin, 15 received carboplatin, 27 received gemcitabine, 20 received cetuximab, 4 received cisplatin + cetuximab, 4 received carboplatin + cetuximab, and 1 received carboplatin + panitumumab.

One hundred thirty-two patients had bilateral neck irradiation, eleven (nine of group A) had unilateral neck irradiation, and in four patients (all of group A), the lymph nodes were not irradiated. Patients in group A received a median dose to the PTV of 66 Gy (range 58–66 Gy, in 2 Gy per fraction), and those in group B a median dose of 69.12 Gy (range 26–70 Gy, in 2 or 2.16 Gy per fraction).

Two patients discontinued HT, one after 64 Gy because of grade 4 skin toxicity in a protocol with induction TPF and cetuximab followed by HT with concurrent weekly cisplatin and cetuximab and one after 62 Gy because of grade 3 oropharyngeal toxicity with hyperventilation-induced syncope (in a protocol of HT with concurrent weekly cisplatin). Six patients died during HT (one in group A, five in group B): one death from rapidly progressive disease (+euthanasia), one death by suffocation (alcohol), three unexpected deaths at home, and one death that seemed clearly treatment-related (skin + mucosal toxicity and pulmonary complications). All three patients who died unexpectedly at home (aged 52, 56, and 65) were treated with combined modality therapy for locoregionally advanced SCCN (1 concurrent chemoradiotherapy [CCRT] with carboplatin, 1 CCRT with cisplatin, and 1 with TPF induction followed by bioradiotherapy [BRT]). All three were heavy smokers, had uninterrupted HT, had grade 3 mucositis when seen last by the radiation oncologist (the day of death in 2, 3 days earlier in 1), needed tube feeding, and had risk factors (cardiac and pulmonary).

Acute Toxicity

Acute toxicity scoring revealed grade ≥ 3 toxicity of the skin (19%), mucosa (76%), swallowing (45%), pain (40%), and grade 2 xerostomia (54%); 43% (19% in group A, 52% in group B) required a feeding tube or total parental nutrition during HT. Detailed information about these toxicities related to the given treatment modality in group A and group B are summarized in Tables 3 and 4, respectively. Clearly, the addition of drug therapies to HT increased toxicity. Grade ≥ 3 mucosal toxicity and severe swallowing problems increased with more additional ST (61% and 10% with HT alone, 70% and 46% with CCRT/BRT, and 92% and 72% with IT + CCRT/BRT, respectively). The *p* values for grade ≥ 3 mucosal toxicity and swallowing problems are 0.4049 and 0.004 for HT versus CCRT, 0.0002 and <0.0001 for HT versus IT + CCRT, and 0.0180 and 0.0199 for CCRT versus IT + CCRT, respectively. This was also reflected in an increased weight loss, in particular in group B (median weight loss 4% and 9% with HT alone and HT + ST, respectively, *p* = .004), and in the numbers of necessary feeding tubes (Table 4).

Late Toxicity

Late toxicities in relation to treatment in group A and group B are summarized in Tables 5 and 6. After a median follow-up of

Table 1. Patient and tumor characteristics

Characteristic	Group A (n = 42)	Group B (n = 105)	Total (n = 147)
Age: median (range)	60 (16–88)	61 (46–89)	61 (16–89)
Gender: male/female	32/10	82/23	114/33
PS (WHO): 0/1/2	24/16/2	54/44/6	78/60/8
Unknown	0	1	1
Smoking: yes/no	35 (83%)/6	93 (89%)/12	128 (87%)/18
Unknown	1	0	1
Pack years: median (range)	30 (0–65)	39 (0–80)	35 (0–80)
Unknown	7	19	26
Tumor site			
Oral cavity	25 (59%)	8 (8%)	33 (22%)
Oropharynx	5 (12%)	42 (40%)	47 (32%)
Hypopharynx	0	20 (19%)	20 (14%)
Larynx	12 (29%)	35 (33%)	47 (32%)
Tumor grade: 1/2/3	14/22/6	21/54/16	35/76/22
Unknown	0	14	14
Primary tumor stage			
I	3 (7%)	1 (1%)	4 (3%)
II	7 (17%)	23 (22%)	30 (20%)
III	12 (29%)	13 (12%)	25 (17%)
IV	20 (48%)	67 (64%)	87 (59%)
Unknown	0	1 (1%) ^a	1 (1%) ^a

^aTxN1, stage III or IV.

Abbreviations: PS, performance status; WHO, World Health Organization.

Table 2. Treatment modalities

Treatment	Group A	Group B	All
S + RT	22	0	22
S + CCRT	19	0	19
RT	0	17	17
CCRT	0	39	39
BRT	0	2	2
IBT + BRT	0	1	1
ICT + BRT	0	15	15
ICT + S + BRT	1	0	1
ICT + CCRT	0	18	18
ICT + BCRT	0	2	2
IBCT + BRT	0	1	1
IBCT + CCRT	0	3	3
IBCT + BCRT	0	7	7
All	42	105	147

Abbreviations: BCRT, biochemoradiotherapy; BRT, bioradiotherapy; CCRT, concurrent chemoradiotherapy; IBCT, induction biochemotherapy; IBT, induction biotherapy; ICT, induction chemotherapy; RT, radiotherapy (helical tomotherapy); S, surgery.

44 months, the presence of grade ≥ 2 late toxicities after HT + ST was approximately twice that observed with HT alone for skin (27% vs. 13%, $p = .1124$), subcutis (34% vs. 13%, $p = .0204$), pharynx (30% vs. 13%, $p = .1021$), and larynx (10% vs. 3%, $p = .0569$). Grade ≥ 2 mucosal toxicity in both groups combined was present in 29%, whereas for xerostomia this was 40%. Interestingly, further analysis of the group B patients showed that grade ≥ 2 xerostomia almost doubled when IT was

added to the treatment (Table 6, $p = .0393$). Treatment-related permanent percutaneous endoscopic gastrostomy (PEG) tubes in both groups combined were still present in 2.6% of patients treated with HT alone and in 7.1% of those treated with HT + ST ($p = .4407$).

Radiation Treatment Time

The RTT in groups A and B related to the treatment modalities used is summarized in Table 7. More than half of the patients (55%) evaluable at the end of HT had their HT RTT prolonged by 3 days or more. A prolongation of the RTT by 5 days or more was found in 34 patients (24%), equally divided between groups A and B. The main reasons for these prolonged RTTs were maintenance of the machine (1 day every 5 weeks), machine breakdown (estimated downtime of 3%), and holidays. Whenever practically possible, treatment delay was compensated for by a twice-a-day irradiation on another day of the same week. Only 2 patients had a prolongation of the RTT of more than 10 days: 1 because of meningitis and 1 because of grade 4 toxicity (skin + mucosal toxicity) and pulmonary complications. The first patient died 4 years after his treatment for a stage IV supraglottic carcinoma (surgery followed by HT) of a SPT of the liver. The second patient died during HT + cetuximab for stage IV carcinoma of the cheek.

Treatment Efficacy

The group A patients were all in clinical complete remission after treatment. At the time of analysis, 15 patients (36%) had died: 6 of a SPT, 3 of distant metastasis, 2 of a locoregional recurrence, 1 of aspiration pneumonia, and 3 of nontumor related causes.

Table 3. Severe acute toxicity and selective supportive care measures in group A

Acute toxicity	RT (n = 22)		CCRT ^a (n = 20)	
	Grade 3	Grade 4	Grade 3	Grade 4
Skin	3 (14%)	0	1 (5%)	1 (5%)
Mucosa	15 (68%)	0	15 ^a (75%)	0
Xerostomia	na	0	na	0
Pharynx	2 (9%)	0	4 (20%)	0
Larynx ^b	0	0	0	0
Pain	5 (23%)	0	6 (30%)	0
Weight loss	0	0	1 (5%)	0
Fentanyl ^c	10 (45%)		8 (40%)	
PEG ^c	3 (14%)		5 (25%)	

^aIncluding one patient with induction chemotherapy followed by surgery and bioradiotherapy.

^bNine patients with a laryngectomy were excluded from laryngeal toxicity analysis (one RT, eight CCRT).

^cGrading system not applicable on Fentanyl and PEG.

Abbreviations: CCRT, concurrent chemoradiotherapy; na, not applicable; PEG, percutaneous endoscopic gastrostomy (feeding tube); RT, radiotherapy (helical tomotherapy).

In group B, 83 patients (79%) had a clinical complete remission after treatment. Of the remaining 17 patients, 16 had a partial remission, and 1 was progressive from the start. The latter patient died 3 months after CCRT for his T2N0 carcinoma of the larynx. Of the 16 patients with a partial response, 11 underwent salvage surgery and became free of disease, 2 were inoperable, whereas 2 had distant metastases, and 1 refused total laryngectomy. Interestingly, 8 of the 11 patients that underwent salvage surgery failed again locoregionally later on; in 1 case there was a suspicion of that at death, and only 2 patients remained disease-free. Overall, 49 patients (47%) had died; 15 because of locoregional tumor recurrence, 11 because of distant metastasis, 1 because of progressive disease from the start, 5 because of progressive disease after a partial response to primary treatment, 4 as result of a SPT, and 2 because of treatment-related causes. In 9 patients, no obvious direct relationship with tumor progression or treatment could be found, and in 2 patients the cause of death was possibly tumor-related.

The 2- and 3-year EFS and OS probabilities and the 2- and 3-year LRF, DF, and SPT rates for all patients and for groups A and B separately are depicted in Figures 1–3, respectively. Further analysis of the 81 (77%) stage III/IV patients of group B who received combined modality treatment showed an EFS and OS probability at 3 years of 54% and 62%, respectively, whereas LRF, DF and SPT rates were 26%, 16%, and 3%, respectively. In this subgroup, there were no striking differences in OS and in EFS between the patients treated with CCRT/BRT alone and those treated with IT + CCRT/BRT (Fig. 4).

The results of a simple and a multiple Cox regression model in the function of overall survival can be found in Table 8. Prolongation of the RTT, as was applied in our study, did not show an impact on survival. Smoking and grade are significant prognostic factors in the univariate analysis, but only the prognostic meaning of the severity of smoking was retained in the multivariate model. Of the smokers, 30% died

of primary tumor-related causes versus only 6% of the nonsmokers.

DISCUSSION

In this retrospective analysis of 147 patients with SCCHN, we found the use of HT feasible not only when used alone as definitive treatment or postoperatively but also when combined (in 73%) with different forms of contemporary systemic therapies. Acute grade 4 toxicities occurred infrequently (5%), and only 2 patients (1%) stopped HT early for acute toxicity. One patient died during treatment, and it was considered to be a treatment-related death (<1%). However, 3 additional patients (2%) died at home during the treatment period, and no explanation could be found. Our 4% early mortality (2.7% potentially treatment-related) is in concordance with the 0%–5% early death rates (death occurring during treatment until 1 or 2 months after treatment), as reported in a cross-comparison of clinical trials in SCCHN patients treated with CCRT [38]. Three patients (one in group A, two in group B) died of late complications that might have been related to treatment (i.e., 2% in group B patients, 2% overall). These latter figures compare favorably to an earlier reported RTOG analysis on late toxicities with conventional RT techniques, mostly two-dimensional planning and delivery (see below) [7].

It is clear that the addition of chemotherapy and/or anti-epidermal growth factor receptor monoclonal antibodies during HT preceded or not by IT increased the incidence of acute and late toxicity (see below). However, another additional factor might have had a negative influence on the toxicity observed in this study: the rather large lymph node RT volumes treated with high doses of HT, including not only the involved lymph node region but also the neighboring lymph node levels and even the high risk parts of the node-negative neck, as has been our daily practice until January 2010.

The most important radiotherapy-related acute toxicity was mucositis, followed by xerostomia, swallowing problems, and pain. The most important radiotherapy-related late toxicity was xerostomia, followed by toxicity to the subcutis, the skin, and the pharynx. Severe (grade ≥ 3) acute mucosal toxicity and swallowing problems increased with more additional ST (61% and 10% with HT alone, 70% and 46% with CCRT/BRT, and 92% and 72% with CCRT/BRT + IT, respectively), and a similar pattern was observed for the late toxicities. The toxicity observed in the present cohort of patients was very much comparable with the toxicity we observed in a previous cohort of 78 patients treated between 2003 and 2007 in our radiotherapy center with static beam IMRT [39]. However, it is of interest to note that the present cohort of patients included substantially more patients treated with radiation plus ST than in that previous cohort (73% vs. 45%, respectively). Therefore, we looked specifically in 30 of the 78 patients having tumors of the comparable disease sites, that is, larynx, oral cavity, oropharynx, and hypopharynx, that were treated with RT alone. This showed 6% more grade 3 dermatitis in the present study (13% versus 7%) and 35% less grade 3 mucositis (62% versus 97%). Our findings of late toxicity (40% grade ≥ 2 xerostomia, $\pm$ 25% grade ≥ 2 toxicity in subcutis, skin, and pharynx) correspond well with the findings of Kong et al. [40] using HT in 30 head and neck cancer patients (in 14 cases with concurrent mostly cisplatin-based chemotherapy, but without ICT) in a mixed patient group, among whom 33% had nasopharynx cancer.

Table 4. Severe acute toxicity and selective supportive care measures in group B

Acute toxicity	RT (n = 17)		CCRT/BRT ^a (n = 41)		IT + CCRT/BRT ^b (n = 47)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Skin	2 (12%)	0	6 (15%)	1 (2%)	12 (25%)	2 (4%)
Mucosa	9 (53%)	0	28 (68%)	1 (2%)	43 (91%) ^{c,d}	0
Xerostomia	na	0	na	0	na	0
Pharynx	2 (12%)	0	24 (59%) ^c	0	34 (72%) ^e	0
Larynx	3 (18%)	0	10 (24%)	1 (2%)	9 (19%)	0
Pain	2 (12%)	1 (6%)	16 (39%)	0	28 (60%) ^f	1 (2%) ^f
Weight loss	0	0	0	0	3 (6%)	0
Fentanyl ⁱ	7 (41%)		26 (63%)		32 (68%)	
PEG ⁱ	3 (18%)		22 (54%) ^g		30 (64%) ^{c,h}	

^aConsisting of platinum with or without anti-EGFR MoAbs in 68%, gemcitabine in 27%, and cetuximab alone in 5%.

^bConsisting of platinum with or without anti-EGFR MoAbs in 40%, gemcitabine in 26%, and cetuximab alone in 36%.

^cp value versus RT < 0.01.

^dp value versus CCRT/BRT < 0.01.

^ep value versus RT < 0.001.

^fp value versus RT < 0.01 for grades 3 and 4 combined.

^gp value versus RT < 0.05.

^hOne patient with IT + BRT got total parenteral nutrition.

ⁱGrading system not applicable on Fentanyl and PEG.

Abbreviations: BRT, bioradiotherapy; CCRT, concurrent chemoradiotherapy; EGFR, epidermal growth factor receptor; IT, induction treatment; MoAb, monoclonal antibody; na, not applicable; PEG, percutaneous endoscopic gastrostomy (feeding tube); RT, radiotherapy (helical tomotherapy).

Table 5. Late toxicity related to therapy in group A

Late toxicity	RT (n = 22)			CCRT ^a (n = 19/20 ^b)		
	Grade 3	Grade 4	Grade ≥2	Grade 3	Grade 4	Grade ≥2
Skin	0	2 (9%)	4 (18%)	1 (5%)	0	7 (37%)
Subcutis	0	0	4 (18%)	2 (11%)	0	5 (26%)
Mucosa	0	1 (4%)	4 (18%)	2 (11%)	0	5 (26%)
Xerostomia	0	0	6 (27%)	2 (11%)	1 (5%)	7 (37%)
Pharynx	1 (4%)	0	3 (14%)	6 (32%)	0	7 (35%)
Larynx ^c	0	0	1 (5%)	0	1 (9%)	2 (18%)
Pain	0	0	3 (14%)	2 (11%)	0	5 (26%)
Permanent PEG ^e	0			2 (11%)		
Pneumonia ^e	2 (9%)			1 (5%) ^d		
Median follow-up time (months, range) ^e	47 (10–67)			49 (8–61) ^b		

^aOne patient with induction chemotherapy followed by surgery and bioradiotherapy.

^bOne patient who died during RT was excluded from late toxicity analysis.

^cNine patients with a laryngectomy were excluded from laryngeal toxicity analysis (one RT, eight CCRT).

^dOne patient with total laryngectomy died of aspiration pneumonia.

^eGrading system not applicable on Permanent PEG, Pneumonia, and Median follow-up time.

Abbreviations: CCRT, concurrent chemoradiotherapy; PEG, percutaneous endoscopic gastrostomy (feeding tube); RT, radiotherapy (helical tomotherapy).

Generally, comparison of the present HT data to prior data, particularly from IMRT studies, is difficult because randomized comparison of both techniques are nonexistent, and patient populations in the reported studies are very heterogeneous, whereas assessment and scoring of toxicity, both acute and late, are quite variable [41]. However, in one retrospective study comparing HT with static beam IMRT, the patient groups and toxicity scoring systems were quite similar to those in our present study [42]. That study analyzed 149 patients, 53 treated with static beam IMRT (53% with concurrent chemotherapy), and 96 treated with HT (65% with concurrent chemotherapy). No major differences were observed between the two patient groups with respect to mucositis and nonmucositis acute side effects. They reported 17% grade 3 late dysphagia in both

groups, tube feeding dependency at 1 year (8% with IMRT, 13% with HT), and grade 2 or more xerostomia (10% with IMRT, 8% with HT) as late toxicity finding, data completely in line with the observations in our present study.

Our late toxicity results compare favorably with those reported by Machtay et al. [7] analyzing a subset of three previously reported RTOG trials of CCRT as primary therapy for locally advanced SCCHN (RTOG 91-11, 97-03, and 99-14), all using non-IMRT techniques. Overall, 43% of the assessable patients in that study had severe late toxicity, 27% had grades 3–4 toxicity to the pharynx, 20% had >2 years feeding tube dependency, and there was 10% treatment-related death. In comparison, our group B patients treated with combined modality therapy (CCRT/BRT with or without IT) showed only

Table 6. Late toxicity related to therapy in group B

Late toxicity	RT (<i>n</i> = 17)			CCRT/BRT ^a (<i>n</i> = 35/41 ^b)			IT + CCRT/BRT ^c (<i>n</i> = 45/47 ^b)		
	Grade 3	Grade 4	Grade ≥2	Grade 3	Grade 4	Grade ≥2	Grade 3	Grade 4	Grade ≥2
Skin	0	0	1 (6%)	2 (6%)	0	8 (23%)	5 (11%)	0	12 (27%)
Subcutis	1 (6%)	0	1 (6%)	3 (9%)	0	9 (26%)	7 (16%)	0	20 (44%) ^d
Mucosa	3 (18%)	1 (6%)	6 (35%)	1 (3%)	0	7 (20%)	1 (2%)	1 (2%)	18 (40%)
Xerostomia	4 (24%)	0	5 (29%)	6 (17%)	0	12 (34%)	3 (7%)	0	25 (56%)
Pharynx	0	0	2 (12%)	3 (9%)	0	6 (17%)	7 (16%)	0	17 (38%)
Larynx	0	0	0	0	0	2 (6%) ^e	1 (2%) ^e	0	5 (11%) ^e
Pain	0	0	2 (12%)	2 (6%)	0	3 (9%)	3 (7%)	0	6 (13%)
Permanent PEG ^g	1 (6%)			1 (3%)			4 (9%)		
Pneumonia ^g	6 (35%)			11 (31%)			6 (13%) ^f		
Median follow-up time (months, range) ^g		42 (14–66) ^b			47 (7–62) ^b			44 (8–62) ^b	

^aConsisting of platinum with or without anti-EGFR MoAbs in 68%, gemcitabine in 27%, and cetuximab alone in 5%.

^bPatients who died within 6 months after RT were excluded from late toxicity analysis.

^cConsisting of platinum with or without anti-EGFR MoAbs in 40%, gemcitabine in 26%, and cetuximab alone in 36%.

^d*p* value versus RT < 0.05.

^eOne patient with a salvage laryngectomy was excluded from late laryngeal toxicity analysis.

^fOne patient died of repetitive pneumonia.

^gGrading system not applicable on Permanent PEG, Pneumonia, and Median follow-up time.

Abbreviations: BRT, bioradiotherapy; CCRT, concurrent chemoradiotherapy; EGFR, epidermal growth factor receptor; IT, induction treatment; MoAb, monoclonal antibody; na, not applicable; PEG, percutaneous endoscopic gastrostomy (feeding tube); RT, radiotherapy (helical tomotherapy).

Table 7. Treatment and outcome in early and advanced stage squamous cell carcinoma of the head and neck

Group	Treatment	<i>n</i>	Stage		Response				Recurrence					Death	RTT
			I–II	III–IV	CR	PR	PD	+	<i>n</i>	LR	M	LR + M	SPT		
A	S + RT	22	10	12	22	0	0	0	1	0	0	1	4	5	45 (38–53)
	S + CCRT	19	0	19	18	0	0	1	4	2	2	0	4	9	46 (39–49)
	IT + S + BRT	1	0	1	1	0	0	0	1	1	0	0	0	1	43
	Subtotal	42	10	32	41	0	0	1	6	3	2	1	8	15	45 (38–53)
B	RT	17	15	2	16	1	0	0	3	2	1	0	2	8	46 (43–55)
	CCRT/BRT	41	9	32	31	5	1	4	11	5	5	1	3	17	47 (18–54)
	IT + CCRT/BRT	47	0	47	36	10	0	1	18	8	3	7	4	24	48 (35–54)
	Subtotal	105	24	81	83	16	1	5	32	15	9	8	9	49	47 (18–54)
Total		147	34	113	124	16	1	6	38	18	11	9	17	64	

Abbreviations: +, death during radiotherapy; BRT, bioradiotherapy; CCRT, concurrent chemoradiotherapy; CR, complete response; IT, induction therapy; LR, locoregional; M, metastasis; *n*, number; PD, progressive disease; PR, partial response; RT, radiotherapy (helical tomotherapy); RTT, radiation treatment time; S, surgery; SPT, second primary tumor.

grade 3 (no grade 4) late pharyngeal toxicity in 12.5% and feeding tube dependency in 6%.

Overall, 43% of our patients at one time during treatment or within 6 months thereafter needed some form of enteral or parenteral nutrition, in particular those receiving combined modality treatment. Interestingly, only 17% of group A (vs. 57% in group B) needed this. The explanation for this difference most likely is multifactorial; as a result of the lymph node dissections in group A, (bilateral) neck irradiation could be avoided in 31% of these patients, and there was also a predominance of oral cavity cancers in group A (in both conditions it is easier to spare the swallowing apparatus); other factors are the lower radiation dose and the fact that no additional use was made of IT in that subgroup.

All the toxicity, both acute and late, should be properly dealt with to avoid a rapid deterioration of the patient's

condition and to avoid a fatal outcome. This requires a particular knowledge and a well-equipped facility. Therefore we strongly recommend that head and neck cancer (HNC) patients who need to be treated with combined modality therapy are referred to specialized centers with experience in high-tech HNC radiotherapy [43].

Several studies have indicated that the overall treatment time (OTT) has a major impact on outcome in head and neck cancer, and in fact each additional day is considered to have a deleterious effect [44, 45]. Recently it was found in a retrospective analysis of the TAX 324 study that in the induction chemotherapy setting, the RTT was significantly associated with survival, and that the OTT, after adjusting for RTT was not [46]. The authors acknowledged that their study most likely did not have a large enough spectrum of OTT values to see a significant effect after

Figure 1. Event-free and overall survival and locoregional failure, distant failure, and second primary tumors for all patients. Abbreviations: 2nd prim, second primary tumor; CI, confidence interval; DF, distant failure; EFS, event-free survival; LRF, locoregional failure; OS, overall survival.

Figure 2. Event-free and overall survival and locoregional failure, distant failure, and second primary tumors for group A. Abbreviations: 2nd prim, second primary tumor; CI, confidence interval; DF, distant failure; EFS, event-free survival; LRF, locoregional failure; OS, overall survival.

adjusting for RTT. In our study, although 24% of our patients had a prolongation of 5 days or more (mostly because of machine maintenance and/or holidays), we did not find a significant impact of this delay on outcome. However, median RTT both in group A and in group B patients ranged from 45 to 48 days, as clearly indicated in Table 7.

Efficacy data, as obtained in this retrospective analysis, are difficult to compare with data from nonrandomized trials performed by others because patient selection and cross-trial comparisons are frequently a source of confusion. Nevertheless, it is of interest to note that our 2-year LRC of 82% and 2-year OS of 72% are very much in agreement with the results in a smaller group of patients treated in another Belgian institute (and most likely in patients with a similar Belgian signature) [47]. In that study, 14% of the 63 treated patients received HT in the postoperative setting, 29% received HT + ST, and 75% had stage

III or IV disease. They reported a 2-year LRC of 77% and a 2-year OS of 66%. Efficacy results are also difficult to compare with results from randomized trials, in which only patients are included who fulfill the clearly defined selection criteria for these studies. Our patients comprised an unselected group, patients were referred for postoperative radiation because they had unfavorable characteristics in the pathology specimen or needed radiation with or without ST as primary therapy for resectable or unresectable or inoperable disease. Overall, they had a human papillomavirus (HPV)-negative profile (although p16 staining was not a routine procedure at that time in our institute), that is, in great majority they were heavy smokers (median number of pack years, 35), of older age (35% were 65 years or older), approximately 50% had a performance status of 1 or 2, and many of them suffered from comorbidities (although this was not routinely scored). Despite that, our

Figure 3. Event-free and overall survival and locoregional failure, distant failure, and second primary tumors for group B. Abbreviations: 2nd prim, second primary tumor; CI, confidence interval; DF, distant failure; EFS, event-free survival; LRF, locoregional failure; OS, overall survival.

Figure 4. Overall survival and event-free survival in function of the treatment given for stage III and IV patients in group B (comparing CCRT/BRT and IT + CCRT/BRT). Abbreviations: BRT, bioradiotherapy; CCRT, concurrent chemoradiotherapy; IT, induction therapy.

results were favorable in comparison with the 2-year survival data in randomized trials in the HPV-negative cohorts, which range from 48% to 68%, and HPV unknown patients treated with CCRT or CCRT preceded by TPF range from 57% to 61% [48–50].

The survival curves of the patients with stages III and IV of group B treated with CCRT/BRT alone versus those treated with CCRT/BRT preceded by IT did not suggest a major difference between the two approaches (Fig. 4). This is in line with the results of recently reported randomized trials studying the role of induction chemotherapy in addition to CCRT, but in disagreement with the most recently reported Italian trial, which claimed a beneficial effect on survival by using a TPF regimen in addition to CCRT/BRT [51–54]. It is merely speculative in trying to explain why we did not find a difference

between the two approaches; there were certainly a significantly higher number of stage IV patients in the group treated with IT than in the group treated with CCRT/BRT alone (96% vs. 71%, $p = .0053$). Moreover, the percentage of patients treated with BRT was higher in the IT + CCRT/BRT group than in the CCRT/BRT group (36% vs. 5%, $p = .0005$). Taking into account that a recent meta-analysis suggested that cisplatin-based CCRT is associated with a better overall survival compared with BRT (RT + cetuximab), this might be an additional factor negating any beneficial effect of induction chemotherapy in our patient population [55].

We are aware of the shortcomings of a retrospective analysis. In addition, some patients were referred to our radiotherapy unit from partner hospitals in the region, the selection of whom might have been beyond our control (e.g.,

Table 8. Simple and multiple Cox regression model in function of overall survival

Characteristic	Number	Simple Cox regression model			Multiple Cox regression model ^a		
		HR	95% CI HR	<i>p</i>	HR	95% CI HR	<i>p</i>
Gender							
Female	33	0.85	0.46–1.57	.607			
Male	114						
Age in years (mean [S.D.])	61 (11)	1.01	0.98–1.03	.488			
PS (WHO)							
1/2	68	1.06	0.65–1.74	.819			
0	78						
Smoking							
Yes	128	3.28	1.03–10.46	.045			
No	18						
Pack years ^b							
Median (Q1–Q3)	35 (19–45)	1.03	1.01–1.04	.0003	1.03	1.01–1.04	.0006
Primary site				.209			
Oropharynx	47	1.26	0.63–2.52	.510			
Hypopharynx	20	1.91	0.88–4.13	.099			
Larynx	47	0.89	0.43–1.83	.474			
Oral cavity	33						
Stage							
III/IV	113	1.25	0.68–2.30	.474			
I/II	34						
Grade				.095			.537
3	22	2.33	1.00–5.39	.049	1.69	0.67–4.25	.269
2	76	1.85	0.92–3.73	.085	1.34	0.61–2.97	.470
1	35						
Surgery							
Yes	42	0.68	0.38–1.22	.196			
No	105						
Induction treatment							
Yes	48	1.37	0.38–2.27	.217			
No	99						
CCRT							
Yes	108	1.64	0.89–3.01	.114	1.42	0.73–2.76	.305
No	39						
RTT (days) ^c				.536			
≥5	34	1.32	0.75–2.49	.307			
3–4	43	1.37	0.69–2.52	.410			
<3	64						

^aMultiple Cox regression model selected based on simple models ($p < .15$ is included in model).

^bMissing data for 26 patients.

^cSix patients who died during HT were omitted.

Abbreviations: CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio; PS, performance status; Q, quartile; WHO, World Health Organization.

if they were lost to follow-up after IT or surgery or patients who received surgery but did not need adjuvant HT). Moreover, a large variety of treatment options has been applied in this patient cohort, late toxicity was not always scored at the same time after HT, and at that time there was no information on HPV status. However, the present study is a reflection of the daily practice in Europe and therefore of interest to other centers because the data most likely mirror

reality more than the selected populations in randomized trials [13, 38].

CONCLUSION

Our observations indicate that the use of HT alone or in combination with ST is feasible and promising and has a low late fatality rate. However, late toxicity is substantially higher when ST is added to HT. Because this combined modality

approach is appropriate for a large proportion of HNC patients, it seems advisable to deliver such treatments in specialized centers.

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