New techniques in radiation therapy for head and neck cancer: IMRT, CyberKnife, protons, and carbon ions. Improved effectiveness and safety? Impact on survival?

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The objective of this study was to assess the comparative effectiveness of intensity-modulated radiation therapy (IMRT), conformal and two-dimensional radiation therapy, proton beam, and carbon ion therapy in terms of tumor control and survival on the one hand and adverse events and quality of life on the other in irradiated head and neck cancer patients. A search of the literature was performed. At a given time, innovative techniques in radiation therapy may appear superior to routine irradiation techniques and clinical trials may therefore be considered unethical. IMRT, because of its superiority in terms of dose distributions and potential to preserve the salivary glands, has gradually replaced two-dimensional and conformal irradiation in routine use. The PARSPORT phase III trial is one among the rare trials to randomize two-dimensional and conformal irradiation against IMRT. It showed a 50% reduction in late xerostomia. Similarly, the relevance of clinical trials to prove the superiority of protons compared with photons is highly controversial. Although the expected benefit of particle beam therapy on dose distributions, local control, and quality of life seems sufficient for routine use without phase III trials, it should be noted that new toxicity profiles might be seen as was the case for IMRT (posterior alopecia, anterior mucositis, uncertainties of integral dose, and secondary cancers). Prospective clinical and medico-economic assessment, possibly in phase II trials, is therefore critically needed along with stringent quality assurance programs. Technological advances in radiation therapy clearly provide a benefit for patients despite the lack of level I evidence. *Anti-Cancer Drugs* 22:596–606 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Head and neck cancers account for approximately 5% of cancers in the United States and 48 000 new cases yearly, with an estimated 11 300 deaths. The main challenge in radiation therapy for head and neck cancer is to attain the highest probability of tumor control or cure with the least amount of morbidity and toxicity in normal surrounding tissues. Tissues sensitive to radiation and associated with clinically meaningful toxicities are referred to as 'organs at risk'. Radiotherapy is used both as a primary modality and as an adjuvant treatment after surgery. Radiation therapy has been mostly based on photons (and electrons) in the last 50 years. More recently, several institutions have been equipped with particle beam therapy equipment delivering protons or carbon ions. New irradiation techniques are made possible by improvements in production technologies (including optimization of photon-based facilities with linear accelerators (LINAC) for modulated arctherapy, or dedicated computed tomography (CT)-based TomoTherapy (TOMO), stereotactic radiation therapy including CyberKnife–Novalis ExacTrac and cyclotrons/synchrotrons for ion-based treatments; Fig. 1), informatics, in particular for treatment planning (intensity-modulated techniques with devices allowing for modulation of particle fluency and treatment planning systems allowing for inverse planning) and imaging with image-guided radiation therapy (IGRT). The main treatment modalities use standard fractionation (one fraction per day for 5–7 weeks) or modified fractionation schemes, either hypofractionated with doses per fraction between 2.5 and 3.0 Gy or accelerated or hyperfractionated radiotherapy. The benefits of these innovative radiation techniques and equipment for clinical practice on tumor control, survival, toxicity, and quality of life (QOL) endpoints are discussed below. The level of evidence is limited because of the lack of randomized studies comparing the old and new irradiation techniques [1]. However, there are several advantages as discussed below.

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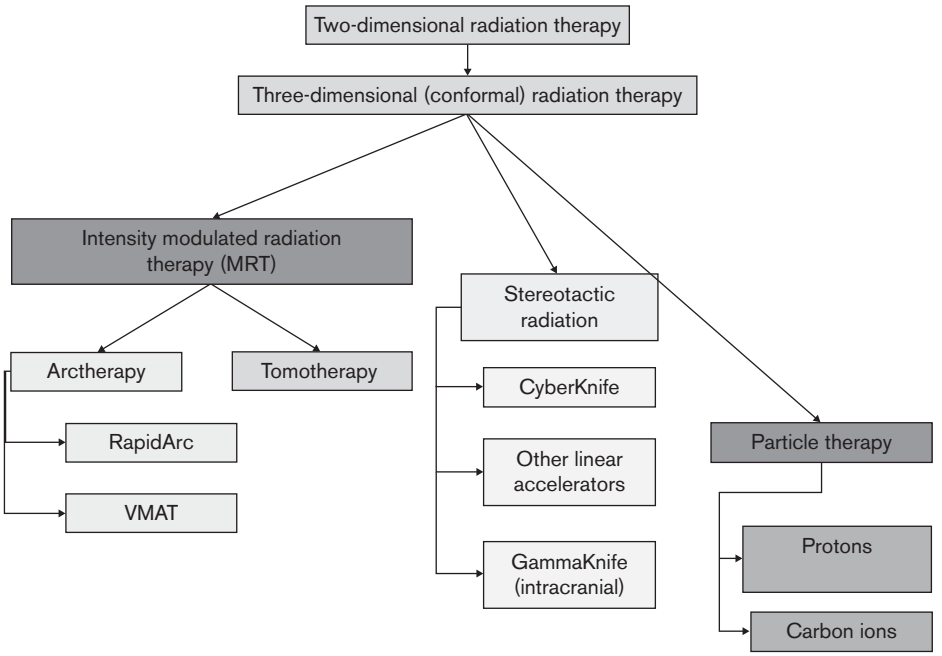
Fig. 1



Irradiation techniques, brief overview of the techniques discussed in the manuscript. VMAT, volumated intensity modulated arc therapy.

Equipments used for conventional radiation therapy and IMRT

Most deep head and neck tumors (skin tumors in the head and neck area excluded) are treated with photons. Cobalt-60-based equipment produces monoenergetic γ-rays (with rather superficial dose distributions) but have been abandoned since the 1990s for radiation protection and dosimetric reasons and replaced by LINAC using electrons accelerated to produce X-rays. Compared with cobalt radiation, LINAC can produce photons at higher energy that are permitted to treat deeper tumors while sparing the skin. As each beam continues on its path beyond the tumor, the use of multiple beams means that a significant volume of normal tissue receives a lower dose. Electrons are the most widely used forms of radiation for superficial tumors, and because the depth of penetration can be well controlled by the energy of the beam, it is possible to spare the underlying normal structures.

Radiation therapy has evolved from two-dimensional to three-dimensional photon-beam or combined (photons and electrons) techniques. Two-dimensional radiotherapy uses simple ballistics (field number, direction, and shape) established from the two-dimensional fluoroscopic simulation of bony anatomy-based images and manually made metal blocks for isodose shaping. Three-dimensional conformal radiotherapy (CRT) is based on CT with the delineation of target volumes and organs at risk (OARs) and machine-driven beam-shaping devices use multileaf collimators (MLC), that is, metal leaflets. These automated MLCs move swiftly during irradiation to ensure that the dose coverage tightly conforms to the target. Two-dimensional and CRT use forward planning to create radiation dose distributions. The International Commission on Radiation Units and Measurements created a terminology to standardize tumor volume definitions for CRT planning. The definitions include gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). GTV pertains to gross disease identified by clinical work-up (e.g. physical examination and imaging). The CTV includes the GTV and any areas at risk of microscopic disease. PTV includes the CTV with 3–10 mm margins to account for patient/organ motion and day-to-day set-up variation. The treatment plan dose distribution shows how much dose is delivered to the tumor and normal structures using both dose–volume histograms and isodoses on axial slices or reconstructed images.

Potential of IMRT for improvement of the therapeutic ratio in head and neck cancer

Intensity-modulated radiation therapy (IMRT) has been used since 1995. Unlike CRT, IMRT uses inverse planning determined by the desired radiation dose distribution to the tumor and dose constraints to normal surrounding structures and OARs. It is particularly interesting for irregularly shaped concave tumor targets near normal tissues. MLCs allow for the modulation of the intensity of radiation within each field, thus yielding

better target coverage and potentially reducing the radiation dose to normal structures. MLCs may be moved while the beam is stopped with the step-and-shoot technique or during irradiation using the sliding window technique. Besides these advantages, it is worth noting that patients may receive a higher total body volume irradiated at low doses with IMRT, there is decreased dose homogeneity and increased risk of a marginal miss because of rapid dose fall-off outside the target volumes (in which case, local relapse may occur). Set-up reproducibility and accurate daily patient immobilization is therefore critical. Changes in patient anatomy such as weight loss, tumor, or parotid shrinkage must be accounted for to conform the initial treatment plan and may require replanning during the course of treatment if changes are significant (adaptive radiation therapy). IMRT is time-consuming in terms of delineation (thinner CT slices, determination of volumes critical because of steep dose gradients) but may be compensated by the use of automatic segmentation tools (atlases) in the near future. Although initially time-consuming, the treatment planning (dosimetry, quality assurance) and delivery steps are becoming quicker with increasing experience. IMRT is usually delivered with conventional fractionation (30–35 fractions) for a total dose of 60–70 Gy in 6–7 weeks and five daily 20-min fractions weekly. Some teams use a simultaneous integrated boost (SIB), which delivers a slightly superior dose in the tumor volume (usually 2.12–2.2 instead of 2 Gy) and accelerates the treatment (shortens the duration of radiotherapy to 6–6.5 weeks). More often now, IMRT is used from the very beginning of the treatment course with the so-called SIB technique. For each fraction of treatment, the subclinical (undetected but microscopically present) spread of cancer cells in the broad head and neck area is treated with a relatively lower dose (with at least 1.6 Gy per fraction), while the primary tumor is irradiated simultaneously with a higher dose. The total dose received at any structure of interest varies. Its subsequent clinical effect can vary widely depending on the fractionation schemes used and the association with chemotherapy. Total physical doses are less meaningful than the quantitative biological correction for the intercomparison of treatment results using different IMRT ± SIB techniques. Furthermore, IMRT introduces dose inhomogeneity within a specific structure because of modulation. The biological and clinical consequences because of such an effect are yet poorly understood. However, a recent area of interest is dose painting, which can deliver a radiation boost to hypoxic regions as identified, for example, on functional imaging. These issues, and the effects of relatively slow dose rates as in IMRT [2] are at the forefront of clinical radiation oncology research currently and the art of implementing IMRT is continually being refined.

Radiation is associated with acute (during and up to 3 months post radiation) and late toxicities, which can have a deleterious effect on the patients' QOL. Chemoradiation may be associated with even higher toxicities (particularly mucositis and xerostomia) [3]. Treatments can affect basic functions such as chewing, swallowing, breathing, tasting, smelling, hearing, and can significantly alter appearance and voice. Most frequent acute toxicities are mucositis, dysphagia, xerostomia, dermatitis, and pain. Significant late radiation-induced toxicities include grade 2 + xerostomia [4] (60–90% incidence), grade 3 + dysphagia [4] (15–30%), grade 3 + osteoradionecrosis (ORN) of the jaws [5] (5–15%), sensori-neural hearing loss [6] (40–60%), skin fibrosis, and laryngeal cartilage necrosis. Late radiation toxicity can be permanent and results in reduced QOL for the patient [7]. The benefits of IMRT might be questionable in the absence of randomized studies. In contrast, it may be considered unethical not to use the higher level of sophistication and randomized trials between IMRT and CRT have had difficulty in enrolling patients despite the relevance of the question (GORTEC 2004-01).

IMRT versus conventional two-dimensional radiotherapy/CRT

There is direct evidence that IMRT versus two-dimensional radiotherapy is in favor of IMRT (Table 1). Eight out of nine IMRT studies reported significant benefits of IMRT with differences of more than 40% [13–15] on survival and better QOL. Comparative effects for other adverse events have not been sufficiently addressed to draw conclusions but a benefit is expected for most side effects because of better conformality. It allows for greater sparing of normal structures such as salivary glands, upper aerodigestive tract mucosa, optic nerves, cochlea, pharyngeal constrictor muscles, brain stem, and spinal cord [16,17]. Very few randomized trials comparing IMRT, CRT, and two-dimensional radiotherapy have been published [4,14,18]. These included fewer than 100 patients each. Two trials included nasopharyngeal cancer patients and one oropharyngeal and hypopharyngeal cancer patient only. IMRT-based salivary gland sparing in various head and neck subsites has been shown in three randomized phase III trials [19]. The multicenter study (PARSPORT; ASCO 2009) compared parotid sparing IMRT with two-dimensional radiotherapy in patients with oropharyngeal and hypopharyngeal cancer. It showed a significantly reduced rate (40 vs. 74%) of grade 2 or more xerostomia (Late Effects of Normal Tissue/Somatic Objective Management Analytic Scale) in the IMRT arm at 1 year post radiotherapy [4]. Two phase III randomized controlled trials, investigating parotid gland sparing using IMRT for patients with nasopharyngeal cancer showed similar results [14,18,20]. This also translated into better QOL. Studies by Kam *et al.* [14] and Pow *et al.* [18] selected patients with only stage I/II disease while Nutting *et al.* [4] included patients with 77% of stage III/IV disease. Kam *et al.* compared primary IMRT and primary two-dimensional radiotherapy, but

Table 1 Intensity-modulated radiation therapy

Auteur	Patients	Tumor subsite	Median dose, range	Definitive or postoperative	Concurrent chemotherapy (%)	Median follow-up, range (months)	Toxicity	Locoregional control	Overall survival	Remarks
Chen *et al.* [8]	77	All	SIB 66, 60–72 Gy	Both	62	21, 3–29	nc	2 year (77%)	2 year (82%)	
Farrag *et al.* [9]	63	All	SIB 60–70.5 Gy	Both (19% postoperative)	29	25, 19.4–28	nc	2 year (77%)	2 year (66%)	
Kodaira *et al.* [10]	20	Nasopharynx	SIB 70, 66–70 Gy	Definitive	90	10.3, 3–17	G3 xerostomia (0%)	nc	10 months (95%)	
Moon *et al.* [11]	51	All	SMART 60–64.8 Gy	Postoperative	4	32, 5–78	Acute G3 dermatitis (10%) Acute G3 mucositis (10%) Late G3 xerostomia (10%) Late G3 skin reaction (2%)	3 year-LRRFS (75%)	3 year (71%)	SMLC–IMRT (33) and TOMO (18)
Sheng *et al.* [12]	10	Oropharynx	SIB 70 Gy	Definitive	100	nc	Acute G3 dermatitis (0%) Acute G3 mucositis (10%) G3 xerostomia (0%)	18 months (80%)	18 months (67%)	

IMRT, intensity-modulated radiation therapy; LRRFS, locoregional relapse free survival; nc, not communicated; SIB, simultaneous integrated boost; SMLC, segmental multileaf collimator-based IMRT; SMART, simultaneous modulated accelerated radiation therapy; TOMO, TomoTherapy.

both groups included some patients who did and did not receive intracavitary brachytherapy. Accrual in the GORTEC 2004-01 trial has been slow and 70 patients have been included to date. In addition, five observational studies reporting on rates of late xerostomia all favored IMRT [4,21–24] with differences (δ) ranging from 7 to 79%. Three studies reported on QOL related to xerostomia including dry mouth, sticky saliva, and swallowing and all favored IMRT. IMRT also enables sparing of the pharyngeal constrictor muscles and therefore has the potential to reduce acute and late radiation-induced dysphagia. By virtue of its ability to spare the cochlea, IMRT also has the potential to reduce radiation-induced hearing loss. The significant increase in the burden of toxicity resulting from radiotherapy can be reduced using IMRT. It is noteworthy that the data are not conclusive, in particular for ORN and skin toxicity with differences between complication rates of 3–6%. The rates of acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late ORN, and bone toxicity were reported in several observational studies and typically favored IMRT, but differences were not consistently statistically significant. Studies on acute skin toxicity are not conclusive. No conclusions on tumor control or survival could be drawn. The single randomized, controlled trial had too small sample size and too short follow-up to ascertain differences in tumor control or survival [4]. In principle, IMRT offers advantages over CRT and two-dimensional radiotherapy because it is more conformal and may therefore allow better tumor coverage and dose escalation [25]. In using IMRT to treat patients with head and neck cancer, theoretical dose delivery advantages should translate into improved therapeutic outcomes. As there is potential to introduce small errors at each step, IMRT quality assurance programs are strictly endorsed during the whole treatment planning process: from delineation of tumor volumes (operator performance [26] and standardization becoming even more of age [27,28]), to replanning in case of tumor shrinkage and from care in patient positioning to verification of dose delivery. In a phase I dose escalation study using IMRT with concomitant cisplatin in patients with stage III and IV squamous cell carcinoma (SCC) of the larynx/hypopharynx, dose escalation was safe and tolerable [29]. The 2-year locoregional control was higher for dose-escalated patients. There was no other significant late toxicity. Although the patient numbers are small, and the follow-up short, the results are encouraging and justify further investigation.

Interestingly, new nonlimitating toxicity profiles have appeared with IMRT in the beam paths in structures that were not defined as OARs [30]. Such profiles include posterior alopecia, nauseas because of irradiation of the area postrema [31] and anterior mucositis [32] (30 Gy).

In contrast to the situation in the United States, where widespread implementation of IMRT started in 1990–1995, IMRT is being currently implemented in a rapidly

growing number of centers across Europe with one trend and a dilemma: should these centers start 'conventional IMRT' or switch without transition from CRT to modulated arctherapy or TOMO. These alternative techniques proposed in routine clinical use are optimizations of IMRT. Each IMRT fraction lasts for approximately 20 min; for example, twice that of a two-dimensional/three-dimensional fraction and there are, in general, 30–35 fractions for one head and neck treatment. Arc techniques and rotational IMRT techniques have thus been designed to deliver IMRT in a faster way, namely intensity-modulated arc therapy (IMAT), volumated intensity modulated arc therapy (VMAT) or TOMO. Verification can be done by applying special phantoms in which radiochromic film is positioned for an IMAT treatment, or radiographic films. IMRT-like distributions are obtained in a single (or sometimes with two arcs) rotation of the gantry, varying the gantry speed and dose rate during delivery in contrast to standard IMRT, which uses fixed gantry beams. This technique has been implemented in several treatment planning software. Machines such as RapidArc from Varian Medical Systems (Palo Alto, California, USA) or VMAT from Elekta (Stockholm, Sweden), among others, have been installed in many institutions in recent years. Planning studies using arctherapy show shorter planning and treatment time, lesser monitor units for treatment delivery, better dose homogeneity, and normal tissue sparing [33–37]. Data with regard to clinical implementation of this technique are being collected in the clinics. Similar results are expected as with IMRT.

Helical TomoTherapy

Helical TOMO is a recent device delivering IMRT in a helical manner using a rotating 6 MV linear accelerator and a simultaneously moving couch. Beam modulation is obtained with a rotational gantry system and a 64-leaf binary MLC rather than a fixed number of beam angles, as with traditional segmental MLC-based IMRT for radiation delivery. The combination of MLC, field width, and table speed gives a high degree of dose modulation and shaping. TOMO is designed not just as a dedicated IMRT delivery system, but as an IGRT delivery system, thanks to the presence of an integrated online megavoltage CT unit. A xenon ion chamber CT detector system is mounted on the gantry directly opposite to the beam line. This offers two benefits for IGRT: the obvious one being the acquisition of volumetric CT imaging of the patient on the treatment position at the time of treatment delivery with the aim of verifying patient set-up and to reduce margins around target volumes. Second, during treatment the intensity of photons that exit the patient can be collected and used in a back-projection computation to assess the dose distribution that is delivered to the patient. The imaging beams are produced at a lower energy (3.5 MV) than the treatment beams and the output of the guide is reduced. This results in the acquisition of volumetric images at doses comparable with doses required to obtain two-dimensional images on megavolt electronic portal imaging devices [38]. The shape, location, and the extent of head and neck carcinomas make them well suited for TOMO. On comparing IMRT plans with TOMO for head and cancer with those from SLC-IMRT, TOMO was reported to show better quality for dose conformity and homogeneity for PTV and dose sparing of the OARs [39–42]. Although CT imaging with TOMO is not intended to be used to collect diagnostic images, it may have a useful role in treatment planning. Megavoltage CT images obtained using the TOMO treatment machine do not present artifacts (example: dental filling) (because of the different physical processes contributing to the creation of the image) and can be used after registration with a conventional CT scan for the purposes of structure delineation, dose calculation, and treatment planning [43].

Although dosimetric studies suggest a potential to further improve the therapeutic ratio in the treatment of head and neck cancer, few studies have investigated the actual clinical outcomes.

Owing to the impossibility of carrying out the sum of two treatment plans with the TOMO treatment planning system, most teams treating head and neck cancer use a SIB in place of sequential treatment with a successive reduced volume boost. Preliminary results are comparable with those obtained with segmental MLC-based IMRT in terms of tumour control with a locoregional control and an overall survival of 75–80% and 66–82%, respectively, at 2 years [8–12]. Only one published clinical study showed the ability of TOMO to spare the parotid gland and preserve the salivary function [44]. A prospective multicentric French study is on-going to evaluate TOMO and other IRMT techniques (IMAT and VMAT included) to treat head and neck tumors with definitive radiation therapy in terms of cost, disease control, and late toxicities (i.e. xerostomia).

Stereotactic fractionated radiation therapy

For systems such as the GammaKnife, approximately 200 cobalt-60 radioisotope sources emitting γ rays (identical to X-rays) are oriented in a hemispherical manner or in another similar geometrical pattern, and focused on a central point at which the lesion target is placed. The second way of producing such focused radiation is through LINAC that generate X-ray beams from a single electronic source that can be rotated or moved around a central focus. Well-known commercial X-ray systems include CyberKnife, XKnife, Novalis among others. Stereotactic radiosurgery targets must be small (usually 3 cm or less in diameter) and the number of lesions to be treated must be low (usually four or fewer). LINAC-based stereotactic radiation therapy can be used as

a boost for head and neck tumors beyond conventional radiation treatment or to re-irradiate tumors that have failed locally and are inoperable or with positive margins. LINAC-based stereotactic radiation therapy precision can be combined with the biological advantages of fractionation to better spare normal tissues. The CyberKnife has gained popularity because of its capacity to treat cranial lesions noninvasively and to treat mobile extracranial tumors [45]. Owing to its frameless equipment, it can be used for single-session and multi-session radiotherapy. It allows for the delivery of multiple sessions for large tumors with near-critical normal structures. Accuracy is below 1 mm for static targets and approximately 2 mm for mobile targets. In head and neck cancer [46–56], it has been mostly used in the re-irradiation setting and is being increasingly investigated as a boost after more conventional radiation therapy [46], such as IMRT in large prophylactic volumes. Several series of fractionated stereotactic re-irradiation have been reported for recurrent head and neck carcinomas [46–52,55,56]. Complete response rates vary from 9 to 79%. The corresponding 2-year overall survival rates vary from 14 to 41% (Table 2). Heterogeneity among studies is because of various tumor stages, tumor volumes, irradiation doses, earlier treatments, and anatomical sites. In most studies [49,54–56], patients with lymph node metastases were included, but the reported outcomes were indistinctly given whether the patients were with or without lymph node metastases. Kawaguchi *et al.* [56] reported an overall survival of 79% in their patients without lymph nodes, which exceeded all of the survival rates published earlier in the setting of salvage treatment. They also showed that unresectable lymph nodes were the most important prognostic factor and were poorly treated with stereotactic re-irradiation and adjuvant chemotherapy using a 5-fluorouracil prodrug for 1 year [56]. Several institutions, such as the Erasmus Medical Center-Daniel den Hoed Cancer Center in the Netherlands, have developed indications with CyberKnife for a boost in oropharyngeal cancer in comparison with a boost in brachytherapy after external beam radiotherapy. This has been fostered by the observation that despite local tumor control rates of approximately 80% at 5 years, with treatments such as IMRT, 20–40% of patients experience late side effects, such as xerostomia and dysphagia. Definitive results with the CyberKnife boost are awaited. Nomoto *et al.* [51] published some preliminary results with stereotactic irradiation as a boost for adenoid cystic carcinomas (ACC). Owing to the delivery of multiple minibeams, stereotactic irradiation is most appropriate for limited volumes. Therefore, the indications and the large volumes irradiated prophylactically with IMRT in head and neck cancer (nodal levels in particular) cannot be compared with volumes irradiated with stereotactic radiotherapy. Stereotactic radiation appears promising for the re-irradiation of local recurrences. Data on the response in the nodes are contradicting. It has real potential for boost irradiation as an alternative to a boost using brachytherapy or IMRT. It is less invasive than brachytherapy and allows for even steeper dose gradients than IMRT; for example, it may better spare surrounding normal tissues.

Table 2 Stereotactic irradiation-studies on re-irradiation using CyberKnife

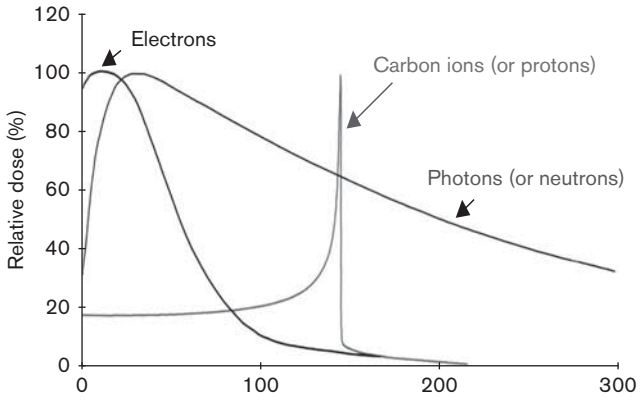
Author	Patients	Median dose/fraction	Median follow-up, range (months)	Median tumor size	Before irradiation dose, median, range	Toxicity	Complete response rate	Overall survival	Remarks
Voynov *et al.* [54]	22	24/1–8	19, 11–40	19, 3–140	98, 70–190 BED10	0 grade 4+	–	2 year (22%)	
Heron *et al.* [47] Heron [48]	25	25–44/5	NS	45, 4–217	66–69	0 grade 3+	9%	1 year (18%)	
Roh *et al.* [55]	36	30/3–5	17.3	23, 1–115	70, 39–134	0 grade 4+, 36% grade 3	43%	2 year (31%)	
Rwigema *et al.* [49]	85	01/05/35	6, 1.3–39	25, 3–162	70, 32–171	0 grade 4+, 5% grade 3	34%	2 year (16%)	
Siddiqui *et al.* [52]	44	13–18/1 or 36–48/5–8	6.8, 1.5–48	16, 2–155	64, 50–74	7% grade 3, 9% grade 4	31%	2 year (14%)	
Unger *et al.* [56]	65	30/2–5	16	75, 7–276	67, 32–120	11% grade 4+	54%	2 year (41%)	
Kawaguchi *et al.* [57]	22	33.7/2–5	24/4–39	25, 3–74	40–65	0 grade 4+, 23% grade 3	45% (N– 64%, N+ 13%)	2 year N– (79%), N+ (13%)	1 year adjuvant 5-FU prodrug
Lartigau *et al.* [58]	50	36/6	6	20, 5–295	58, 18–75	27% grade 4+, 1 toxic death	24%	Crude local control (97%)	29 concomitant cetuximab
Inoue *et al.* [59]	28	32, 20–40/3, 1–8		12		3% grade 3	Most not progressive		
Cengiz *et al.* [60]	46	30, 18–35/5, 1–5				18% grade 3+, 7 toxic deaths by carotid blowout syndrome	27%	Median 1 year	

5-FU, 5-fluorouracil; BED10, biologically equivalent dose; NS, not significant.

Particle therapy (protons and carbon ions)

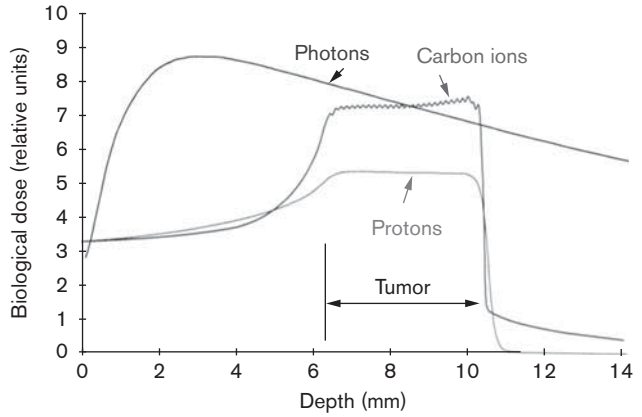
Compared with photon therapy, particle therapy using protons or carbon ions may improve treatment effectiveness and safety in selected head and neck cancers, thanks to their excellent dose distributions superior to those achievable by the highest photons technology and, in addition, for carbon ions, a higher biological effect [61]. Dose distribution is characterized by the absence of an 'exit' dose beyond the target (conversely to photons): the 'Bragg peak' (Figs 2 and 3). This provides a very high potential to reduce acute and late toxicities, especially when radiosensitive organs (i.e. optic pathways, brainstem, and cervical spinal cord) are in close proximity with the tumor targeted volume. It also helps improve local control through higher conformity with the target (limiting the risk of under-dosage) and dose escalation. Moreover, the potential to decrease the volume of normal tissues irradiated with low dose permits decreasing the risk of second malignancies, which may be especially relevant in children.

Fig. 2



Comparative physical properties of photons, electrons, and charged positive particles (protons and carbon ions): physical dose depth distribution. Protons and carbon ions are characterized by the 'Bragg peak'.

Fig 3



Comparative physical properties of photons, protons, and carbon ions: dose depth distribution. Protons and carbon ions are characterized by the 'spread-out Bragg peak', resulting from an addition of elementary Bragg peaks. For a same physical dose carbon ions are characterized by a higher biological effect within the spread-out Bragg peak (the biological effect does not appear within the 'entrance beam' that encompasses the normal tissues).

Carbon ions

Compared with photons and protons, carbon ions are characterized by a higher linear energy transfer, a quantity measuring the rate of energy loss per length of path. For a given physical dose, this property gives to carbon ions a higher biological effect (in terms of cell killing) than the low linear energy transfer radiations, which is estimated by the relative biological effectiveness. This value is especially dependent of the characteristics of the irradiated tissue: two to three for the most normal tissues and cancers known to be 'radiosensitive' (with photons) but can be much higher for radioresistant cancers (i.e. melanoma, ACC, and certain subtypes of sarcoma) [61]. Like photon therapy, both proton and heavy-ion delivery may be optimized with intensity modulation (intensity modulated particle therapy) allowing for 'dose painting' and even repainting, that is, a concept that describes online adaptive irradiation based on the measured delivered dose. Because of their obvious ballistic advantages, protons (and more recently carbon ions) have been considered as the gold standard radiotherapy modality for the base of skull and spinal chordomas and chondrosarcomas. However, their main disadvantages and limitations compared with photons are linked to their high investment cost (and therefore individual treatment cost) of circular accelerators (cyclotrons or synchrotrons) that are required for their production and the size of the equipment and facilities. However, some proton beam equipment is being miniaturized and more and more widely implemented (25 centers in operation and more than 10 planned within the next year). Carbon ion production technology is more recent and has just been industrialized within recent years with only four centers to date in operation in the world (three in Japan; one in Germany), three under construction and several advanced projects. It has also been a matter of debate whether such a high technicity irradiation should be tested within randomized clinical trials [62]. As the expected clinical benefit is unequivocal, most experts consider that it might already be obsolete to compare it with the photons.

Clinical data for head and neck cancers (base of skull tumors such as chordomas and chondrosarcomas excluded) are summarized below for protons and carbon ions (Table 3). Most data for proton therapy in head and neck cancers are issued from the experience of the Massachusetts General Hospital (MGH) [72]. To date,

Table 3 Particle therapy

Author, year, institution	Radiotherapy modality	Number of patients	Localization and stage	Dose (GyE) fractionation (fr)	Median follow-up	Local control and overall survival	Late ≥ grade 3 toxicity
(a) Squamous cell carcinoma							
Slater *et al.* [63] (Loma-Linda)	X+ P (boost)	29	Oropharynx stage III, IV	X: 50.4, 1.8 GyE/fr, P: 25.5, 1.5 GyE/fr. (concomitant boost)	28 months 5 (2–96)	2 year LC: 96% 5 yea LC: 88% 5 year DFS: 65% OS: ND	Three patients: 11%
Mizoe *et al.* [64] (NIRS)	C	19	ND	64, 4 GyE/fr, 4 week or 57.6, 3.6 GyE/fr, 4 week	ND	5 year LC: 70% 5 year OS: 30%	ND
Author, year, institution	Radiotherapy modality	Number of patients	Localization and stage	Dose, total dose; dose per fraction	Median follow-up	Local control–DFS and overall survival	Late ≥ grade 3 toxicity
(b) Adenoid cystic carcinoma							
Schulz-Ertner *et al.* [65] (GSI)	X+C (boost)	29	ACC with skull base involvement	X: 54, 1.8 GyE/fr, C: 18, 3 GyE/fr	16 months	4 year LC: 77.5% 4 year OS: 75.8%	One patient: 3%
Pommier *et al.* [66]	X+P	23	ACC with skull base involvement	76 GyE (accelerated–bid in 19	64 months	5 year LC: 93% 5 year DFS: 56% 5 year OS: 77%	Brain: 10 patients
Mizoe *et al.* [64] (NIRS)	C	107	ACC in the head and neck region	64, 4 GyE/fr, 4 week or 57.6, 3.6 GyE/fr, 4 week	ND	5 year LC: 74% 5 year OS: 68%	ND
Author, year, institution	Radiotherapy modality	Number of patients	Localization and stage	Dose, total dose; dose per fraction	Median follow-up	Local control and overall survival	Late ≥ grade 3 toxicity
(c) Cancers of the nasal cavity and paranasal sinuses							
Truong *et al.* [46][a] MGH	P+X	20	Sphenoid sinus	76 GyE, 1–2 fr/d; chemotherapy: six patients	21 months	2 year OS: 53% 2 year LC: 86%	Nasal Gr2–3: three patients Gr5 CSF leak: one patient
Resto *et al.* [67][a] MGH	P+X	33	Squamous cell carcinoma	71.6 GyE, 1–2 fr/d, P: 57.1%; chemotherapy: 34 patients (30=neuro–endocrine)	43 months	5 year OS: 42% 5 year DFS: 42%	ND
		30	Neuro-endocrine tumors			5 year OS: 69% 5 year DFS: 63%	
		20	ACC			5 year OS: 75% 5 year DFS: 48%	
Fitzek *et al.* [68] MGH	P+X	19	Olfactory neuroblastoma or neuro-endocrine carcinoma	Neoadjuvant chemotherapy High dose proton–photons surgery (three patients) Adjuvant chemotherapy	45 months	5 year OS: 74% 5 year LC: 88% (100% with salvage surgery)	Brain toxicity in five patients (RTOG grade 3 in 1)
Nishimura *et al.* [69]	P	14	Esthesioneuroblastoma	65, 2.5 GyE/fr, 4–5 fr/ week; chemotherapy: five patients	36 months	5 year OS: 93% 5 year RFS: 71%	0
Mizoe *et al.* [70] (2009 update of 2004 study - oral communication)	C	120	Nasal cavity	57.6 or 64 GyE, 16 fr in 4 week	ND	5 year OS: 25.8% 5 year LC: 75.7%	ND
			Parasinus			5 year OS: 44.6% 5 year LC: 63.3%	
Author, year, institution	Radiotherapy modality	Number of patients	Localization and stage	Dose, total dose; dose per fraction	Median follow-up	Local control and overall survival	Late ≥ grade 3 toxicity
(d) Malignant mucosal melanoma (MM)							
Yanagi *et al.* [71]	C	72	MM of the head and neck	52.8–64 GyE, 16 fr, 4 week	49.2 months	5 year LC: 84.1% 5 year OS: 27%	0
Mizoe *et al.* [64]	C+chemotherapy[a]	57	MM of the head and neck	57.6 GyE, 16 fr, 4 week	ND	5 year LC: 85% 5 year OS: 58%	0

CSF, cerebro spinal fluid; DFS, disease-free survival; LC, local control; ND, no data; OS, overall survival; RFS, relapse free survival; RTOG, radiation therapy oncology group.
[a]Concomitant chemotherapy 4 weeks' interval, a total of five courses, two courses before radiation therapy, three courses after radiotherapy.

the highest local control (93% at 5 years) in ACC was reported in the MGH series including 23 patients treated with combined photon and proton protocols (median 76 GyE in 38 days). However, in that series, 10 patients experienced late grade 3 brain toxicities. The experience of the MGH for neuro-endocrine tumors of the sinonasal

tract was first published in 2002 [68] in a series of 19 patients treated with similar radiotherapy protocols and neoadjuvant chemotherapy. In that series, only three patients underwent surgical resection because of poor response to initial chemotherapy. Again, very high local control (88% at 5 years: 100% when including cases salvaged with surgery) and overall survival was reported (74%), however, with five late brain toxicities. The response to chemotherapy was highly predictive for the overall survival outcome. Resto *et al.* [67] analyzed the role of the extent of surgery in the MGH paranasal sinuses in 2007. This series included 30 patients with neuro-endocrine tumors (esthesioneuroblastoma in 21) who experienced a poor response to chemotherapy and were thus subsequently treated with surgery (complete and post-perative radiotherapy in 17 patients and biopsy only in 13 patients). The 5-year overall survival and disease-free survival were 75 and 48%, respectively. The 5-year local control was reported for the subgroup of 21 esthesioneuroblastoma patients: 100% in the case of complete or partial resection and 69% in the case of biopsy alone. The role of protons has also been assessed at the MGH in two small series for nasopharyngeal cancer (17 patients) and sphenoid sinus carcinoma (20 patients) [46,72]. Locoregional control was 79% at 3 years in nasopharyngeal cancer and 86% at 2 years in the series on sphenoid cancers (overall survival was 74% at 3 years and 53% at 2 years, respectively). The role of proton therapy in head and neck SCC has been assessed at the Loma Linda University Medical Center [63]. Twenty-nine patients were included in a phase II study with protons used as a concomitant boost in addition to photons (no chemotherapy) in locally advanced oropharyngeal cancer (76 GyE in 5.5 weeks), resulting in a very high locoregional control rate (84% at 5 years) and disease-free survival (65% at 5 years).

As for carbon ion therapy, the preliminary experience for head and neck malignancies has been published from the National Institute of Radiological Sciences in Chiba, Japan in 2004 [64,70]. This study included 36 patients with miscellaneous histologies (mainly SCC and ACC) and locations (mainly paranasal sinuses and salivary glands) treated in a phase I/II clinical trial using dose escalation. A high 5-year local control was observed for radioresistant histological subtypes. These results have been recently updated. In a series of 19 head and neck SCC patients treated within a phase II study, the 5-year local control was 70% (whereas the overall survival was only 30%) [71]. A large series of 109 ACC patients homogenously treated with carbon ions alone was also presented in 2009. A 74% 5-year local control (and 68% for overall survival) was reported [71]. The most impressive results were obtained for mucosal melanoma with 84% 5-year local control (82% even for large tumor, such as 100 ml or greater), and only two grade-2-mucosal and two grade-2-skin late toxicities [71]. However, the overall survival was poor (27% at 5 years). Yanagi *et al.* [71] recently presented their experience with combined carbon ions and chemotherapy for these patients, resulting in a similar local control and, to date, to a higher overall survival probability (58% at 5 years). The experience of the German Heavy Ion Research Center (GSI) in Darmstadt, Germany, for ACC was published in 2005 [65]. In a series of 29 patients with locally advanced unresectable tumors treated with a combination of photons (IMRT) and carbon ions (boost), the 4-year local control was 78% (similar to those reported in the National Institute of Radiological Sciences series) with only one grade 3 late toxicity. Interestingly, the authors reported their experience of a similar cohort of 34 patients treated with photons alone (fractionated radiosurgery or high-dose fractionated IMRT) during the same period (because of restricted access to the GSI facility). In that prospective (but nonrandomized) comparison, the 4-year local control was only 25% with photons alone ($P = 0.08$).

Vision loss caused by radiation-induced optic neuropathy (RION) is one of the most devastating late complications of radiotherapy for head and neck cancer. Only a few reported studies have evaluated the development of RION after particle therapy. Recently, the Hyogo Ion Beam Medical Center in Tatsuno, Japan, which can provide both proton and carbon ion therapies, reported that the rate of vision loss resulting from RION was 11% at a median follow-up of 25 months and diabetes mellitus was an unfavorable factor for it [73]. Interestingly, there was no significant difference between protons and carbon ions.

The delivery of particle therapy on a wide scale is restricted by the limited availability of particle therapy machines because of the financial resources required. The current role of particle therapy therefore lies in the treatment of tumors close to the skull base or the spinal cord, and in pediatric patients, in whom particle therapy provides maximum benefit in terms of normal tissue sparing. Miniaturization of particle beam equipment will help to promote clinical routine use of particle therapy for head and neck cancers in the next 10 years.

Conclusion

IMRT has become the routine technique for head and neck cancers in many institutions despite the lack of level I evidence because of its ability to spare salivary glands and other functionally important structures or to optimize tumor coverage in locally advanced diseases. It is likely that IMRT will be delivered using arctherapy (rapidity) or TOMO (for large volumes) in the next 10 years. Protons will be delivered in a more limited number of places because of the cost of equipment and will likely be reserved for tumors near critical surrounding structures because of their ballistics advantages. Highly accurate treatment planning will be mandatory to

conform to initial treatment planning to avoid overdosing of the nearby radiosensitive OARs. Carbon ions will be available in a few facilities and will likely be dedicated to radioresistant tumors. These highly conformal techniques have a great potential for improvement of local control. As shown with mucosal melanomas, the benefit on survival is yet to be shown depending on disease characteristics. These techniques allow for better preservation of OARs provided that treatment planning and delivery steps are done very precisely under stringent quality assurance programs. This should be ultimately translated to improved QOL.

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