Chapter 2

RapidArc planning and delivery in patients with locally advanced head and neck cancer undergoing chemo-radiotherapy

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Abstract

Purpose: Volumetric modulated arc therapy (RapidArc,Varian Medical Systems) permits the delivery of highly conformal dose distributions. We studied planning and delivery in patients who underwent RapidArc for locally-advanced head and neck cancer (HNC).

Materials/Methods: A total of 35 consecutive patients who completed RapidArc with concurrent chemotherapy for stages III-IV tumors of the oro- and hypopharynx/larynx in our center were identified. All underwent bilateral neck irradiation and 21 patients had at least N2 disease. A simultaneous integrated boost (SIB) delivered 70 Gy (in 2 Gy/fraction) to the PTV_{boost} and elective nodal regions (PTV_{elect}) received 57.75 Gy. A standard planning constraint set was used and constraints for parotid glands were individually adapted. Treatments were delivered using 2 arcs after all plans were verified in a solid water phantom using GafChromic External Beam Therapy films.

Results: RA planning generally took 1.5-2 hours, which was faster than with our previous 7-field IMRT sliding window technique. Film dosimetry revealed that 0.6% of films exceeded a combination of dose differences ≥3% or distance to agreement ≥2 mm. More than 99% of both PTV's received ≥95% of the prescription dose. Average plan conformity index was 1.13 and mean dose to ipsilateral and contralateral parotid glands were 31.4 Gy, and 26.1 Gy, respectively. The mean beam-on time was <3 minutes and mean number of monitor units was 426.

Conclusions: RapidArc achieved excellent target coverage and normal tissue sparing, with delivery completed in less than 3 minutes. RA is currently our standard IMRT approach for advanced HNC.

Introduction

Head and neck cancer (HNC) accounts for 6% of all malignancies [1,2], and almost half of all patients present with a locally advanced stage. Concomitant chemo-radiotherapy has become the standard of care in such patients as it results in an absolute survival benefit of 6,5% at 5 years compared to radiotherapy only [3]. However, acute and late treatment-related adverse effects are significant[4]. Intensity modulated radiotherapy (IMRT) enables the delivery of highly conformal dose distributions, and increases the therapeutic ratio as target volumes are often large and concave around nearby critical normal tissues. IMRT reduces complaints of dry mouth [5-9] and preliminary reports suggest that lowering the dose to pharyngeal constrictor muscles and larynx could lead to less difficulties with swallowing [10-12], all with comparable or superior locoregional control [13-16].

IMRT planning and quality assurance requirements are generally more complex and time-consuming than 3D conformal treatment planning. A survey in the United States showed substantial variations between the prescribed and delivered IMRT doses [17], indicating the need for good quality assurance.

Guidelines for proper commissioning of IMRT have now been published [18]. Another feature of conventional IMRT plans is the requirement of more machine monitor units (MU) and multiple fixed-angle beams, which in turn leads to longer treatment times [19]. RapidArc (Varian Medical Systems, Palo Alto, CA) is a novel radiation treatment technique which is based on volumetric modulated rotational delivery [20], as opposed to "classic" IMRT which uses fixed gantry beams. By varying the speed of gantry rotation, multileaf collimator shape and continuously changing the fluence (dose rate), RapidArc delivers highly conformal IMRT plans in a short time [19,21,22]. A recent planning study compared single and double RapidArc delivery with our standard 7-field sliding window IMRT in patients with locally advanced HNC [19]. With similar target coverage, double arc plans had higher PTV homogeneity than single arc plans, and both RapidArc plans required less MU and shorter delivery times than conventional IMRT. Consequently, two arc delivery has replaced our all our conventional IMRT.

Some authors have cautioned that there may be tradeoffs between arc techniques which use short treatment times and the quality of dose conformality [23,24]. In order to confirm the findings of our recent planning study, we analyzed RapidArc planning and delivery parameters in a subgroup of HNC patients for whom IMRT plans were technically challenging.

Materials and methods

Patient selection

Between May 2008 and July 2009, a total of 134 patients with head and neck cancer have been treated using RapidArc at our department. In order to evaluate a subset of treatment plans that required a high degree of dose modulation, we analyzed data from the first 35 patients with a primary stage III-IV (American Joint Committee on Cancer, 6th edition) tumor without distant metastases, who also underwent concurrent chemoradiotherapy. Twenty-four patients had oropharynx cancer, 4 hypopharynx cancer and 4 larynx cancer (Table 1). The majority (n=27) received three cycles of concurrent single-agent cisplatinum 100 mg/m2. Five patients received induction chemotherapy (taxotere-cisplatinum-5-FU) followed by weekly cisplatinum at 40 mg/m2 during radiotherapy, 1 patient received weekly cisplatinum only, and 2 elderly patients received concurrent radiotherapy and cetuximab in a schedule described previously [25].

Table 1: patient characteristics

patient	site	stage	TNM	Vol PTV_{elect} (cc)	Vol PTV_{boost} (cc)
1	Oropharynx	IV	T3N2b	515	214
2	Oropharynx	IV	T3N2c	900	414
3	Oropharynx	IV	T2N2b	563	198
4	Oropharynx	IV	T4N2b	947	394
5	Nasopharynx	IV	T2N2	567	206
6	Oropharynx	III	T3N1	812	476
7	Larynx	IV	T4N0	526	144
8	Oropharynx	IV	T4N2c	763	252
9	Oropharynx	IV	T4N1	534	136
10	Oropharynx	IV	T2N2c	553	159
11	Oropharynx	III	T3N0	464	185
12	Oropharynx	IV	T3N2c	709	322
13	Oropharynx	IV	T4N0	522	217
14	Oropharynx	IV	T4N3	907	450
15	Larynx	III	T3N0	708	222
16	Oral cavity	IV	T4N0	493	241
17	Hypopharynx	III	T3N1	731	182
18	Hypopharynx	IV	T4N0	460	141
19	Oropharynx	IV	T2N2c	653	176
20	Oropharynx	IV	T2N2b	664	278
21	Oropharynx	IV	T3N2b	672	270
22	Hypopharynx	IV	T4N3	809	436
23	Oropharynx	III	T3N0	533	254
24	Nasopharynx	IV	T2N2	823	428
25	Hypopharynx	IV	T4N0	588	180
26	Oropharynx	IV	T4N2c	1066	591
27	Oropharynx	IV	T4N2c	959	431
28	Oropharynx	IV	T4N0	447	160
29	Larynx	IV	T1N3	976	506
30	Oropharynx	IV	T2N2b	699	244
31	Oropharynx	III	T3N1	616	188
32	Oropharynx	IV	T4N2c	637	258
33	Larynx	IV	T3N2c	710	122
34	Oropharynx	IV	T4N2b	548	152
35	Oropharynx	IV	T4N0	493	160
Average				673	268
Standard deviation				±168	±125

Abbreviations: TNM = TumorNodeMetastasis (AJCC 6th edition); Vol PTV_{elect} = planning target volume elective nodal regions; Vol PTV_{boost} = planning target volume boost; DVH = dose–volume histogram.

Patients were positioned in a 5 point fixation mask (Posicast® Thermoplastics, Civco Medical Solutions, Kalowa, IA). Gross tumor volume (GTV) was delineated on a contrast-enhanced planning CT scan with 2,5-mm slice thickness. Target volumes were defined in most patients by co-registration of diagnostic MRI scans. Two patients had a planning PET/CT scan. The gross tumor volume (GTV) was defined as the primary tumor and involved lymph nodes on both imaging modalities and examination under anesthesia. The 'boost' clinical target volume (CTV_{boost}) comprised the GTV with a margin of 1 cm, and was corrected for anatomical boundaries. The 'elective' CTV (CTV_{elect}) included the CTV_{boost} and bilateral elective lymph nodes: at least levels II-V, and level I,VI and/or retropharyngeal nodes when indicated and in accordance with published guidelines [26,27]. A margin of an additional 3 mm was taken to create planning target volumes (PTVs).

The organs at risk (OAR) considered for all patients were ipsi- and contralateral parotids, the spinal canal and the brain stem, where appropriate.

Planning objectives and techniques

Dose prescription was set to 57.75 Gy at 1.65 Gy/fraction to the PTV_{elect} and 70.00 Gy at 2.00 Gy/fraction to the PTV_{boost} delivered as a simultaneous integrated boost (SIB). Patients were irradiated once a day, 5 times a week. Plans were generated by a team of dosimetrists experienced in RapidArc planning. A standard constraint set was used for RA optimization, aiming to achieve at least 66.5 Gy (this is 95% of the boost dose) in 99% of the PTV_{boost} and 54.86 Gy (this is 95% of the elective dose) in 98% of the PTV_{elect}, while keeping the boost and elective volumes receiving 107% of their prescribed dose as small as possible, preferably under 1% for the boost. The maximum doses specified for the spinal canal and the brain stem were 46 Gy and 54 Gy, respectively. Four dose objectives were set for parotid glands (PG) and adapted for each patient according to the position of the PG with regard to the PTVs. No specific constraints were used for the other healthy tissues, but a 1cm thick ring was created around the PTVs and 3 constraints were used to to enforce a steep dose fall-off outside the target volumes (Table 2).

Table 2: Constraint set

target volume	min dose (Gy)	max dose (Gy)	priority
$PTV_{elective}$	57	58.5	120-130
PTV_{boost}	69	71	120-130
spinal cord		36-46 (*)	125
brain stem		44-54 (*)	125
shoulders		20	75
standard ring	DVH (**)		90-110
parotids	DVH (**), adapt during first iterations		75

(*) In the initial phase, max dose on spinal cord (brainstem) was set at 46 (54) Gy. This later was changed to 36 (44) Gy since the objectives were mostly easily met.

(**)Three dose objectives were set for the standard ring. Four dose objectives were set for parotids and adapted for each patient according to the position with regard to the PTVs.

Optimization and dose calculation was performed using the Eclipse treatment planning system (version 8.2.23, Varian Medical Systems, Palo Alto, CA) with 6 MV photon beams from a Varian 2300 linac with the Millennium 120-multileaf collimator. The Anisotropic Analytical Algorithm (AAA) photon dose calculation algorithm was used with calculation grid was set to 2.5 mm. Details of the RapidArc delivery process were as described previously [19]. In brief, 2 complementary coplanar arcs of 358° (one counterclockwise (CCW), one clockwise (CW)) were used. A sequential approach was used, in which the first arc plan was used as a base dose plan for the second arc plan which compensated for possible under- or overdosage in the first arc plan, leading to a homogeneous dose in the PTV.

Quantitative evaluation of plans was performed by means of Dose-Volume Histograms (DVH). To appreciate the target coverage in the areas where the PTV approaches the surface, a local virtual build-up of 6 mm (to overcome dose build-up under the skin) was used for optimization and quantification of the PTV coverage. After approval of the plan, the virtual build-up was removed and the dose distribution was recalculated for the actual treatment. A Conformity Index (CI), which is defined as the ratio between the patient volume receiving at least 95% of the prescribed boost dose and the volume of the PTV_{boost} was calculated for all plans. In addition, the boost and elective volumes receiving at least 95% of the prescribed doses (V95), as well as the V107 were registered. The dose to 99% and 95% of the target volumes (D99 and D95, respectively) was also calculated.

Quality assurance

QA was performed as described previously [19]. Briefly, dose distributions were analyzed using a 23 cm cube of polystyrene slabs. This phantom has multiple drawers for insertion of Gafchromic® External Beam Therapy films at different positions, so dose verification can be done in multiple planes during a single treatment session. Dose verification of RA plans was measured for the combination of the two arcs in at least 3 coronal planes throughout the phantom, and this was compared to the calculated dose of the same patient plan.

To ensure a correct patient set-up, in 20 patients, two orthogonal on board kV-images (OBI, Varian Medical Systems, Palo Alto, Ca) were performed prior to each of the first 3 fractions, and the mean shift in 3 dimensions was calculated. From the fourth fraction onwards, patient positioning was systematically done according to the calculated shifts. In 15 patients with PTVs close to critical structures (e.g. the spinal cord or brainstem), daily online set-up was performed based on OBIs or cone beam computed tomography scans.

Toxicity assessment

Patients were all included in a standardized follow-up program with weekly evaluation by the radiation oncologist and scoring of acute toxicity according to the Radiation Therapy Oncology Group (RTOG) Radiation Morbidity Scoring Criteria [28].

Results

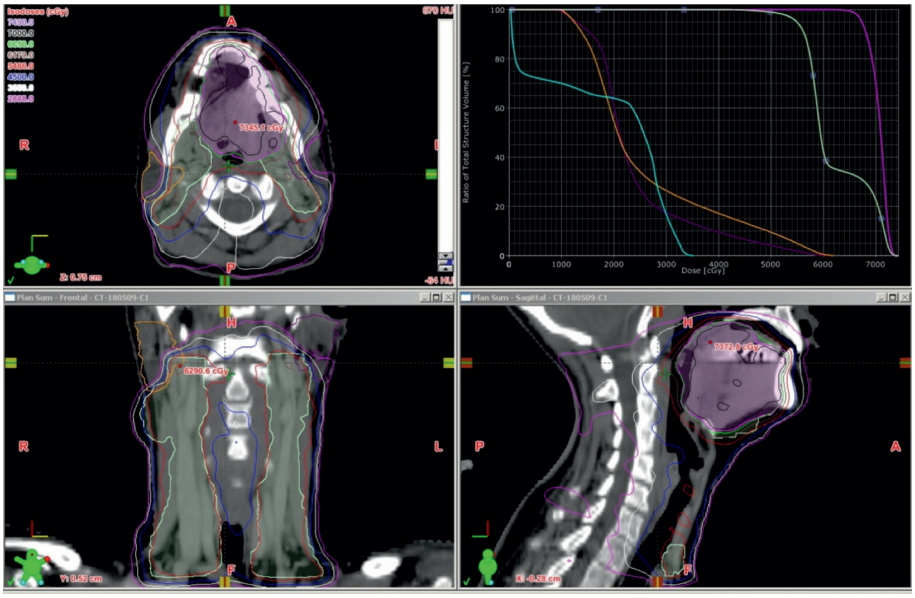
Dose calculations, monitor units and delivery time

Since implementation of a new technique implies a learning curve, exact times for optimization and planning were not registered for each patient. At present, the constraint set can be adapted to an individual patient in 10 minutes, and the actual optimization takes 20 minutes per arc, followed by 20 minutes for dose calculation, which allows for a total process time of less than 2 hours. The mean total MU per fraction of 2 Gy was 426 (range 230-519), and the beam-on time of an individual arc was between 70 and 75 seconds, resulting in an actual treatment time (first beam on till last beam off) of less than 3 minutes. Patients with daily OBI verification had a time slot of 15 minutes; the other patients had a 10 minutes time slot (except for the 3 first fractions when OBIs were performed, the time slot was 15 minutes).

Target coverage

Dose distributions for a representative patient are shown in Figure 1. The mean PTV coverage, CI and OAR doses for all 35 patients are summarised in Table 3. The mean volumes of the PTV_{total} and PTV_{boost} were 673 cm^3 and 268 cm^3, respectively. Despite the generally large tumours, RapidArc achieved very conformal plans with an average CI of 1.13 (standard deviation (SD) ± 0.09). Coverage of both PTV_{elect} and PTV_{boost} was excellent, with on average >99% of both PTVs receiving ≥ 95% of the prescription dose. Only 0.07% of PTV_{boost} received >107%. For the boost volume, D99 was 66.9 Gy, and D95 was 68.3 Gy. For the elective volume, D99 was 55.0 Gy and D95 was 56.9 Gy.

Figure 1



Dose distribution and dose–volume histogram (DVH) for a typical patient with oropharynx tumor. DVH of planning target volume elective nodal regions (PTV_{elect}) in light green, PTV_{boost} in magenta, left parotid glands (PG) in purple, right PG in orange, spinal cord in blue

Table 3: Results

Site (n patients)	V95 Elect (%)	V95 Boost (%)	CI	V107 Boost	Dmean IL PG	Dmean CL PG	Dmax spinal canal
Average oropharynx (24)	99	99.2	1.14	0.075	34.4	27.6	45.3
Average hypopharynx (4)	99	99.2	1.1	0.075	27.4	19.9	44.3
Average larynx (4)	98.9	99.3	1.13	0	19	22.1	47.1
Average other (3)	99.6	97.6	1.12	0	29.5	27.1	48.5
Average all patients	99.01	99.04	1.13	0.06	31.4	26.1	45.7
Standard deviation			±0.09	±0.18	±10.0	±7.0	±4.2
Range					15.9-53.6	12.3-37.6	34.3-50.1

Abbreviations: V95 elect (%) = % elective volume receiving 95% of the elective dose (= 54,86 Gy); V95 boost (%) = % boost volume receiving 95% of the boost dose (= 66,50 Gy); CI = conformity index: Vol 66,50 Gy / Vol PTV boost; IL PG = ipsilateral parotid gland; CL PG = contralateral parotid gland.

Organs at risk

The maximum cord dose was on average 45.7 Gy (range 34.3-50.1 Gy, SD ± 4.2 Gy). One patient received a dose maximum of 50.1 Gy. The latter was accepted as we had delineated the canal and not the spinal cord itself, and as only a small portion of the canal (<0.5%) received the higher dose. The mean dose to the ipsilateral PG was 31.4 Gy (range 15.9-53.6 Gy, SD 10.0 Gy), and 26.1 Gy to the contralateral gland (range 12.3-37.6 Gy, SD ± 7.0 Gy) (Table 3).

Quality assurance

Film measurements showed that only 0.6% of the films exceeded a combination of dose differences ≥3% or distance to agreement ≥2 mm. For 2 out of 35 patients, more than 2% of the film surface exceeded a dose difference ≥3% or distance to agreement ≥2 mm.

Acute toxicity

In patients with head and neck cancer who will undergo concomitant chemo-radiotherapy, it is generally our policy to place a percutaneous endoscopic gastrostomy tube (PEG-tube) before the start of the

treatment. This did not take place for 6 patients, either due to the decision of the treating physician or to patient refusal. All but one patients with a PEG-tube actually used the device. A total of 10 patients experienced RTOG grade 3 cutaneous toxicity (moist desquamation). Half (17) of all patients had a confluent mucositis (RTOG grade 3 toxicity) and 23 patients required opioid analgesia. Thirty patients had a xerostomia grade 2 toxicity with markedly altered taste and 3 patients with a larynx tumor experienced a grade 3 laryngeal toxicity.

All patients completed the planned radiotherapy. Five of the patients who received cisplatin 100/m2 did not receive the last planned dose of chemotherapy due to either hematological or renal toxicity. Of the 4 patients receiving induction chemotherapy, 2 patients did not complete the 7 cycles of concomitant cisplatin as a result of either hematological or renal toxicity.

Discussion

RapidArc is a novel technique, based on volumetric modulated arc therapy, and planning studies in different tumor types have reported that plan quality is at least comparable to standard IMRT, but with a shorter planning and delivery time and less MU [19,21,22,29]. To the best of our knowledge, this is the first report on the clinical experience with this technique in a larger cohort of HNC patients.

In order to evaluate the use of this technique for the planning and delivery of highly conformal plans, our study focused on patients with locally advanced stage HNC who required bilateral neck irradiation while undergoing concurrent chemotherapy. In 35 consecutive patients, the total process of plan optimization and calculation took less than 2 hours. This is in contrast to our former 7 field IMRT planning that took between 2 and 5 hours, mostly because of reoptimization trying to further improve the obtained dose distribution [19]. Of note, the optimization process had rarely to be repeated for RapidArc plans. For the delivery of a 2 Gy fraction, the mean number of MU in the entire cohort was 426 MU, a considerably lower figure than the average of 1075 MU of a 39 treated patients with HNC who were treated at our center using a 7 field IMRT technique [30]. A 60% reduction in MU will thus lead to a lower dose to the rest of the body with a possible reduction of the risk of secondary cancers [31,32].

Although initially some doubts have been expressed about the clinical use of singe arc therapy [23], our data indicated that a double arc achieved very conformal plans with a CI of 1.13, having a mean dose to ipsilateral parotid gland of 31.4 Gy, and 26,1 Gy to the contralateral parotid gland. This finding is similar to that observed in our recent study showing a significant reduction in radiation-induced morbidity in patients with predominantly, but not exclusively, locally- advanced stage HNC who were treated with IMRT [30]. In this series, the mean dose to the ipsilateral parotid was 28.7 Gy and 23.3 Gy to the contralateral gland, which is not statistically different from our results.

Our use of double arc RapidArc plans in order to achieve a more homogeneous PTV coverage merits comment [24]. When compared to use of single arc plans, double arc RapidArc plans ensured more

homogenous PTV coverage, but required only 5% more MU and treatment delivery took only 75 seconds longer. When verification procedures (OBI, CBCT) were done, time slots of 15 minutes were appointed; for treatment alone, time slots of 10 minutes were calculated. In 15 patients who had tumor nearby critical structures or who had a large inter-fraction variation of their set-up, daily online imaging (with 15 minutes time slots) was used to ensure a correct treatment position. This is in contrast to our previous experience when patients with HNC patients who were treated with a static 7 field IMRT plan had a 20 minute time-slot. Our ability to reduce the machine time for most patients undergoing RapidArc delivery has improved departmental efficiency, leaving more time for imaging and verification procedures.

The improvement in survival achieved using concurrent chemo-radiotherapy [3] comes at the price of increased toxicity. Even though we used an elective dose of 57.75 Gy in 1.65 Gy per fraction, 50% of the patients in the present cohort eventually developed grade 3 mucositis and all but 5 patients used some form of tube feeding. Skin toxicity was mostly mild, only 10 patients experienced moist desquamation. The toxicity observed in these patients who were treated using RapidArc was comparable to the acute toxicity seen in 39 patients who were the subject of a recent study [30]. The follow up of our series is too short to report on late toxicity or survival. However, as the dose distributions are very similar to the conventional IMRT plans, we do not anticipate differences in outcomes. Of the 24 patients with a follow up of at least 6 months, 2 patients have still a PEG tube, 5 patients experience xerostomia grade II (moderate) and 4 patients still use opioid analgesics. One patient had residual tumor after treatment and underwent surgery. Two patients developed distant metastasis (without locoregional recurrence). One patient had a neck dissection because of a regional recurrence 8 months after treatment. All other patients are in complete remission.

In the initial patients, we did not delineate organs at risk other than the PG and spinal cord, but used a ring around the target volumes to enforce a steep dose fall off. Currently, we are using separate constraints for the submandibular glands (if outside the PTV), middle and inner ear (if appropriate) and mandible, as it is desirable to reduce further the doses to these OARs as well. In addition, doses to the constrictor muscles and (supra)glottic larynx may correlate with impaired swallowing and aspiration problems after high-dose radiotherapy [11,33] and we are currently developing a new constraint set trying to lower the dose in these structures.

Conclusion

Delivery of RapidArc plans is possible in less than 3 minutes, achieving excellent target coverage and normal tissue sparing, with acceptable acute toxicity. Planning is faster than our previous 7-field IMRT sliding window technique, and RA is currently our standard treatment approach for advanced stage HNC patients.

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