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ORIGINAL ARTICLE

High Precision Boosting of the Nasopharynx — Dosimetric Comparison of Conventional and Conformal Radiotherapy Techniques

FJ Lagerwaard, PC Levendag, A van Nimwegen, C de Pan, PJCM Nowak

Department of Radiation Oncology, University Hospital Rotterdam – Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

ABSTRACT

Objectives: *We report a 5-year local relapse-free survival of 94% for T1 to 2 nasopharyngeal carcinoma using endocavitary brachytherapy as a boost to deliver cumulative doses of 95 Gy to the nasopharynx. Brachytherapy may be less than adequate for extension of disease into the parapharynx. The aim of the current planning study was to evaluate target coverage and sparing of critical normal structures when boosting the nasopharynx with 3-D conformal external beam radiotherapy, intensity modulated radiotherapy, and fractionated stereotactic radiotherapy in comparison to conventional treatment, i.e. parallel-opposed fields.*

Materials and Methods: *In 17 consecutive patients (12 with limited residual nasopharyngeal carcinoma after external beam radiotherapy, 5 with extensive residual nasopharyngeal carcinoma), computed tomography scans were obtained with the nasopharyngeal brachytherapy applicator in situ. The target volume and normal structures were contoured. Dose distributions were computed for class solutions using parallel-opposed, 3-D conformal external beam radiotherapy and intensity modulated radiotherapy techniques or stereotactic radiotherapy.*

Results: *Adequate target coverage was achieved by all treatment techniques; however, there was an unacceptably high dose to the parotid glands with parallel-opposed fields. Mean dose to the parotid glands was lowest with stereotactic radiotherapy (8.8% ± 3.2%), followed by intensity modulated radiotherapy (12.0% ± 3.2%) and 3-D conformal external beam radiotherapy (14.8% ± 5.0%). The combination of intensity modulated radiotherapy and stereotactic radiotherapy enabled superior parotid gland sparing (6.5% ± 2.8%). The same pattern was found for the 5 patients with extensive residual nasopharyngeal carcinoma.*

Conclusion: *Highly conformal dose distributions with considerable sparing of major salivary glands can be obtained with stereotactic radiotherapy or intensity modulated radiotherapy. As a potential future route, at present we are investigating intensity modulated stereotactic radiotherapy for boosting extensive residual nasopharyngeal carcinoma.*

Key Words: *Conformal radiotherapy, Intensity modulated radiotherapy, Nasopharyngeal carcinoma, Stereotactic radiotherapy*

INTRODUCTION

Radiation therapy, either alone or in combination with chemotherapy is the mainstay of treatment for patients with nasopharyngeal carcinoma (NPC). For early stages, 5 years local relapse-free survival of 94% can be obtained after treatment with external beam radiotherapy (ERT) followed by endocavitary brachytherapy (BT) up to cumulative doses of 95 Gy.[1,2] These high cure rates, however, can only be achieved at the cost of debilitating xerostomia, occurring invariably as a result of early and late radiation toxicity to the major and minor salivary glands.

Radiation treatment schedules for NPC at the University Hospital Rotterdam – Daniel den Hoed Cancer Center have evolved over time. At present (since 1997) the treatment protocol consists of ERT to 60 Gy (T ≤ 2a) or

Correspondence: FJ Lagerwaard, Department of Radiation Oncology, University Hospital Rotterdam, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.
Tel: (31) 10 439 1116; Fax: (31) 10 439 1013;
E-mail: lagerwaard@rtdh.azr.nl

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70 Gy (T ≥ 2b) in 2 Gy/fraction, routinely followed by fractionated endocavitary BT (2 fractions/day, 6 hours interval) of 17 Gy total dose for T stage ≤ 2a (4 Gy - 3 x 3 Gy - 4 Gy/fraction) or 11 Gy for T stage ≥ 2b (4 Gy - 3 Gy - 4 Gy/fraction), using the Rotterdam nasopharynx applicator (RNA). All involved lymph node regions are boosted to a total dose of 70 Gy using high energy electrons. Finally, based on recommendations from our previous analysis,[1] patients with advanced tumour stages (T3-4, N2-3, American Joint Committee on Cancer/International Union Against Cancer [AJCC/UICC] classification, 1997 edition) receive neo-adjuvant chemotherapy. The neo-adjuvant chemotherapy regimen at the present time consists of 3 monthly courses of cisplatin (CDDP) 100 mg/m^2 plus 5-fluorouracil 1000 mg/m^2, 4 days per cycle, for the undifferentiated type NPC, or 6 weekly courses of CDDP 70 mg/m^2 for other grades of histology.

Given the rapid dose fall-off with distance, BT is advocated to be used preferentially in limited disease only: i.e. at the present time in our institution we prefer to limit its use to tumour stages ≤ T2a. For dose escalation in the more advanced tumour stages (≥ T2b), and at the same time sparing of the surrounding critical structures, e.g. the major salivary glands, the use of more complex 3-D external beam treatment techniques are mandatory.

The aim of the current planning study for boosting NPC was to evaluate the relative merits of 3-D conformal external beam radiotherapy (3-DCRT), intensity modulated radiotherapy (IMRT) and fractionated stereotactic radiotherapy (SRT) in comparison to conventional treatment, i.e. parallel-opposed fields. The respective techniques were compared with regard to both target coverage and sparing of critical normal structures, when boosting the nasopharynx after 60 to 70 Gy ERT.

MATERIALS AND METHODS

This dosimetric study was performed using the data of 17 consecutive patients with NPC, referred to the University Hospital Rotterdam – Daniel den Hoed Cancer Center from 1998 to 1999. Pre-treatment tumour classification was performed using the AJCC/UICC classification criteria. Each patient was treated according to the aforementioned protocol guidelines. For all patients, pre-treatment planning computed tomography (CT) scans with the head in a fixation mask were performed and, similarly, after the completion of ERT and insertion of the RNA, CT scanning was performed for BT dose optimisation purposes (Siemens Somatom AR, [Siemens AG Medical Engineering, Computer Tomography, Forchheim, Germany] slice thickness 5 mm, table movement 5 mm). The latter CT scans were used for contouring the boost clinical target volume (CTV) and critical normal structures, including parotid and submandibulary glands, brainstem, spinal cord, and optic chiasma. The CTV for boosting NPC was defined as the nasopharynx proper (Figure 1) with the addition of any residual tumour seen on CT or magnetic resonance imaging (MRI) scan. The 3-D margins used to derive the planning target volume (PTV) from the CTV were 5 mm for conventional planning, 3-DCRT, and IMRT, and 2 mm for SRT, reflecting the immobilisation and repositioning accuracy of the Gill Thomas Cosman (GTC) frame. Conventional treatment planning with parallel-opposed fields (6 MV) was performed using the computer planning system Cadplan (Varian-Dosetek v. 6.0.4, Varian Medical Systems, Helsinki, Finland). The 3-DCRT plans were based on uniform beam profiles using a configuration consisting of 3 non-coplanar 6 MV and 2 non-coplanar 23 MV photon beams ('class solutions'). The Helios (Varian-Dosetek v. 6.0.4) inverse planning module was used for IMRT for the same class solution. Intensity profiles were calculated and optimised for the 'sliding window' technique.

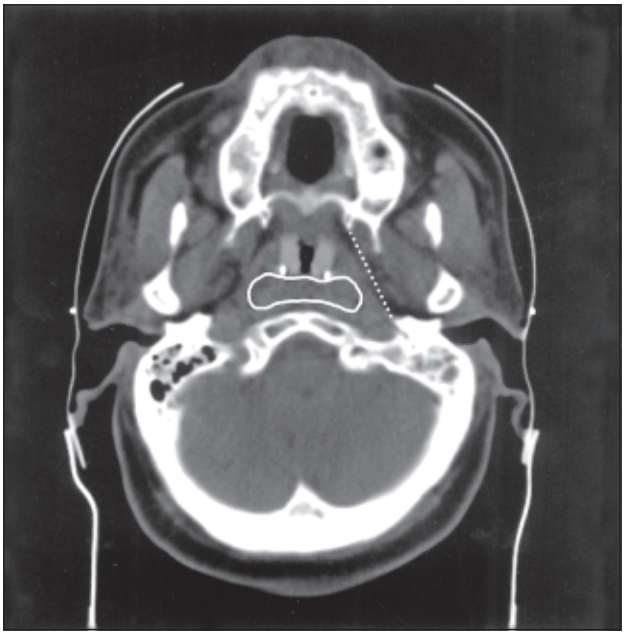

Figure 1. Clinical target volume for a patient with limited residual nasopharyngeal carcinoma (≤ T2a). In some patients, however, the clinical target volume could extend as far as the pterygo-styloid line (one-sided dotted line) of tumours still confined to the nasopharynx proper.

Table 1. Baseline organ constraints for boosting nasopharyngeal carcinoma using Helios inverse planning

	Volume (%)	Maximum dose (%)	PTV constraints for inverse planning	
Planning target volume	-	-	Minimum dose 95%	Maximum dose 120%
Parotid glands	50.0	10.0	NA	NA
	5.5	22.5	NA	NA
	5.0	25.0	NA	NA
Spinal cord	10.0	10.0	NA	NA
	5.0	20.0	NA	NA
Brainstem	10.0	25.0	NA	NA
	5.0	33.0	NA	NA

Abbreviations: PTV = planning target volume; NA = not applicable

The final dose distributions were recalculated using Cadplan v. 6.0.4. The baseline constraints for the PTV and critical normal structures used for IMRT are shown in Table 1. In order to achieve sparing of the contralateral parotid gland in patients with unilateral parapharyngeal extension, the constraints for the ipsilateral parotid gland were omitted, while keeping the overall beam configuration identical. For reasons of comparison, the dose was prescribed to the minimum isodose encompassing the target volume, usually the 80% isodose for SRT and the 90% isodose for IMRT. SRT planning was performed using X-Plan (Radionics, v.2.02, Burlington, USA), i.e. multiple static fields, and using a mini-multileaf collimator. Comparison of treatment techniques was performed with respect to target coverage and sparing of critical surrounding normal structures for both groups, using parameters such as mean dose and V95 (i.e. volume that receives 95% or more of the prescribed dose) taken from dose volume histograms.

Table 2. Patient characteristics

	Sex	Age	Chemotherapy	AJCC/ UICC staging	Stage after ERT
1	M	67	-	T2bN0M0	Limited
2	F	61	+	T1N1M0	Limited
3	M	53	-	T1N0M0	Limited
4	M	66	-	T2bN1M0	Limited
5	M	73	+	T4N2M0	Limited
6	M	65	-	T2bN0M0	Limited
7	M	57	+	T4N2M0	Limited
8	M	48	+	T4N1M0	Limited
9	F	23	+	T2aN1M0	Limited
10	F	60	+	T1N3M0	Limited
11	M	61	-	T2bN2M0	Limited
12	M	59	-	T2aN0M0	Limited
13	F	62	+	T2bN1M0	Extensive
14	F	53	-	T1N0M0	Extensive
15	M	86	-	T2bN2M0	Extensive
16	M	36	+	T4N1M0	Extensive
17	F	40	-	T2bN0M0	Extensive

Abbreviations: AJCC = American Joint Committee on Cancer; UICC = International Union Against Cancer; ERT = external beam radiotherapy.

RESULTS

For analysis of dose distributions, patients were divided into groups with 'limited' (no residual tumour or residual disease confined to the nasopharynx) and 'extensive' residual tumour (tumour extension beyond the nasopharynx into the parapharyngeal space, i.e. past the so-called pterygoid-styloid line, and/or intracranial extension) after ERT. After the completion of ERT, 12 patients were classified as having limited residual NPC and 5 patients had extensive NPC (Table 2).

Limited Residual Nasopharyngeal Carcinoma

From Table 3, it can be seen that adequate coverage of the boost PTV could be obtained with all treatment modalities. With parallel-opposed ERT techniques excellent target coverage could be achieved; however, this was associated with an unacceptably high dose to the major salivary glands. As could be expected from the way the dose was prescribed, dose inhomogeneity within the PTV was largest for SRT, followed by IMRT. Table 3 also shows the sparing capacity of the different treatment techniques with respect to the left (PL-Dmean) and right (PR-Dmean) parotid gland and brainstem (BS-Dmean). For limited tumour extensions (tumour stages ≤ T2a), considerable sparing of both parotid glands could be obtained

Table 3. Boost dosimetry [% (sd)] for limited residual nasopharyngeal cancer, achieved with parallel-opposed fields, 3-D conformal external beam radiotherapy (3-DCRT), intensity modulated radiotherapy (IMRT), and stereotactic radiotherapy (SRT) for the planning target volume (Dmean and V95), right parotid gland (PR-Dmean), left parotid gland (PL-Dmean), and brainstem (BS-Dmean)

	Dmean	V95	PR-Dmean	PL-Dmean	BS-Dmean
Parallel opposed	99.1 (1.2)	97.0 (6.1)	78.8 (14.8)	86.0 (8.3)	9.6 (6.2)
3-DCRT	102.2 (0.3)	98.3 (0.8)	14.8 (5.0)	15.2 (7.8)	21.0 (9.5)
IMRT	99.9 (0.4)	97.8 (1.5)	12.0 (3.2)	10.9 (3.9)	12.4 (3.7)
SRT	119.9 (2.4)	99.1 (0.3)	8.8 (3.2)	8.9 (3.0)	16.8 (3.5)

Table 4. Boost dosimetry [%(sd)] in 4 patients with unilateral parapharyngeal tumour extension, achieved with parallel-opposed fields, 3-D conformal external beam radiotherapy (3-DCRT), intensity modulated radiotherapy (IMRT), and stereotactic radiotherapy (SRT) for the planning target volume (Dmean and V95), ipsilateral parotid gland (PI-Dmean), contralateral parotid gland (PC-Dmean), and brainstem (BS-Dmean)

	Dmean	V95	PI-Dmean	PC-Dmean	BS-Dmean
Parallel pposed	99.6 (0.3)	98.0 (0.8)	85.4 (24.4)	99.9 (1.2)	10.9 (5.3)
3-DCRT	100 (0.3)	98.0 (1.2)	40.0 (7.5)	17.0 (2.4)	22.4 (5.6)
IMRT	99.9 (0.2)	98.0 (0.8)	48.3 (15.2)	11.1 (2.2)	14.7 (1.4)
SRT	115.6 (12.2)	94.3 (9.5)	25.3 (6.8)	14.4 (7.5)	15.3 (3.6)

with SRT, and to a lesser degree with IMRT, followed by 3-DCRT. All treatment modalities achieved this amount of sparing with acceptable doses to critical structures such as the brainstem, spinal cord, and optic chiasma.

Extensive Residual Nasopharyngeal Carinoma

For extensive residual NPC, in particular with unilateral parapharyngeal extension (four patients), all conformal treatment techniques were aimed at maximum sparing of the contralateral parotid gland. The beam configuration of all treatment plans was left unaltered. For each treatment modality, mean dose to the ipsilateral (PI-Dmean) and contralateral (PC-Dmean) parotid gland is shown in Table 4.

In the one patient with an extensive bilateral parapharyngeal tumour after ERT, all treatment techniques were only able to obtain adequate target coverage at the expense of large PTV inhomogeneity, and only SRT was able to achieve parotid sparing below 20%.

DISCUSSION

In view of the highly conformal dose distributions obtained and its ease of application, endocavitary BT is generally the preferred method of boosting the nasopharynx to curative doses.[1-4] The rapid dose fall-off associated with BT enables dose escalation to the nasopharynx, while sparing surrounding critical structures, in particular the major salivary glands. The delivery of high doses to the nasopharynx using conventional parallel-opposed treatment fields is feasible, but will invariably result in xerostomia; in addition, serious complications, including damage to the optic pathways, brain stem, temporal lobes, ear, spinal cord, pituitary gland, and hypothalamus, are not uncommon.[5-9] Recent progress in computerised treatment planning has led to the development of a range of conformal ERT techniques, which may serve as an alternative to endocavitary BT. Improvements in imaging techniques, in particular MRI scanning, have greatly enhanced the ability to accurately determine the extension of the primary tumour region,[10-13] and CT-MRI image fusion may allow for detailed contouring of the nasopharynx. Furthermore, the recently described CT-based definition of lymph node regions in head and neck malignancies[14,15] will facilitate the contouring of clinical target volumes of the upper and lower (elective) neck. With the aid of these tools, reliable use of 3-DCRT has become a realistic option for treatment of patients with NPC. Optimum beam direction and shape can be determined using beam's eye viewing of target volume and critical structures, thereby enabling minimisation of the dose to normal structures. In this study, using a relatively simple class solution consisting of 5 to 6 non-coplanar photon beams for boosting of NPC, the mean dose to the parotid glands could be decreased from 80% to 15% for limited tumour extensions. In patients with unilateral parapharyngeal tumour extension, 3-DCRT could achieve considerable sparing of the opposing parotid gland; however, keeping the mean dose to the brainstem within acceptable limits proved difficult.

IMRT has been shown to offer substantial advantages with respect to sparing of critical surrounding structures for a number of tumour sites.[16-19] Although initially limited to the use of transmission blocks and tissue compensators, improvements in planning systems and treatment machines with multileaf blocking enable the implementation of more advanced IMRT techniques such as 'step and shoot' and 'sliding window' techniques. In the current study, we have used the Helios sliding window technique based on a 3-DCRT class solution. Using this method, we could obtain a modest further decrease in parotid gland dose and, perhaps equally important, a substantial reduction of the mean dose to the brainstem.

SRT for head and neck malignancies was first described by Kondziolka,[20] who used single fraction radiosurgery for recurrent NPC. Since then, the implementation of fractionated SRT has been reported by several authors either as a sole modality for recurrent NPC[21-27] or as a technique for boosting primary disease.[28-30] SRT is

Table 5. Comparison of intensity modulated radiotherapy (IMRT) boost [% (sd)] for limited residual nasopharyngeal carcinoma with standard (5 mm) and stereotactic (2 mm) margins for positioning inaccuracy

	Dmean	V95	PR-Dmean	PL-Dmean	BS-Dmean
IMRT 5 mm	99.9 (0.4)	97.9 (1.5)	12.0 (3.2)	12.2 (3.9)	12.4 (3.7)
IMRT 2 mm	99.8 (0.3)	98.8 (1.6)	6.5 (2.8)	7.2 (2.4)	11.3 (3.5)

Abbreviations: Dmean and V95 = planning target volume; PR-Dmean = right parotid gland; PL-Dmean = left parotid gland; BS-Dmean = brainstem.

characterised by accurate fixation and immobilisation methods, which allow for small treatment margins and a rapid dose fall-off in all directions outside the planning target volume. Our planning study shows the superiority of SRT with regard to sparing of critical normal structures, compared with all other methods. The common practice of dose prescription to the encompassing 80% isodose will, however, result in dose inhomogeneity within the PTV, however, as is the case with BT, this may in fact be advantageous from a radiobiological point of view.[31]

Ongoing developments in sophisticated treatment planning include the incorporation of software for intensity modulation in stereotactic treatment planning systems. This approach could offer a summation of the specific advantages of both IMRT and SRT. In order to simulate intensity modulated radiotherapy for use with stereotactic treatment devices, we recalculated the treatment plans using Helios inverse planning IMRT with (stereotactic) 2 mm margins for positioning inaccuracy, but still with a 1 cm multileaf collimator. From Table 5 it can be concluded that IMRT with stereotactic PTV margins resulted in highly conformal dose distributions, superior to all other techniques. Actual results of IMRT plus SRT will probably be even more conformal, when our department's mini-multileaf collimator with an effective width of 3.5 mm will be used, rather than the 1 cm multileaf collimator used in this simulation. This technique may allow dose escalation without additional morbidity for extensive NPC, i.e. persistent tumour after the completion of ERT, and therefore is likely to improve local control. In fact, as has been suggested previously, those patients requiring a longer than usual time to regress completely carry a significantly higher risk of ultimate local failure compared with immediate complete responders to ERT, if the initial T-stage is T3 or T4.[32]

Although the current planning study shows that significant sparing can be obtained using sophisticated treatment planning systems, due to the low threshold of the major salivary glands for radiation damage[33] this will only be clinically relevant when conformal treatment planning, i.e. at least 3-DCRT, is used from the start of treatment. We are currently investigating options to achieve optimum salivary gland sparing from the start of treatment, i.e. for the large volume disease treated to a dose of 60 or 70 Gy by ERT. The clinical introduction of free radical scavengers such as amifostine, which may substantially increase these threshold levels for clinically manifest xerostomia,[34,35] have underscored the importance of efforts to obtain conformal dose distributions for treatment of NPC.

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