RESEARCH ARTICLE

Neck Node Bolus Technique in the Treatment of Nasopharyngeal Carcinoma with Intensity-modulated Radiotherapy

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Abstract

Purpose: To study the effect of bolus versus no bolus in the coverage of the nodal tumour volume with intensity-modulated radiotherapy (IMRT) for the treatment of nasopharyngeal carcinoma (NPC). Methods and Materials: This retrospective study used data from 5 consecutive patients with NPC who were treated with bolus for large neck nodes using IMRT from November 2011-January 2012 in our institute. All these patients were treated radically with IMRT according to our institution's protocol. Re-planning with IMRT without bolus for these patients with exactly the same target volumes were done for comparison. Comparison of the plans was done by comparing the V70 of PTV70-N, V66.5 of PTV70-N, V65.1 of PTV70-N and the surface dose of the PTV70-N. Results: The mean size of the largest diameter of the enlarged lymph nodes for the 5 patients was 3.9 cm. The mean distance of the GTV-N to the skin surface was 0.6 cm. The mean V70 of PTV70-N for the 5 patients showed an absolute advantage of 10.8% (92.4% vs. 81.6%) for the plan with bolus while the V66.5 of PTV70-N had an advantage of 8.1% (97.0% vs. 88.9%). The mean V65.1 also had an advantage of 7.1% (97.6% vs. 90.5%). The mean surface dose for the PTV70-N was also much higher at 61.1 Gy for the plans with bolus compared to only 23.5 Gy for the plans without bolus. Conclusion: Neck node bolus technique should be strongly considered in the treatment of NPC with enlarged lymph nodes treated with IMRT. It yields a superior dosimetry compared to non-bolus plans with acceptable skin toxicity.

Keywords: Nasopharyngeal carcinoma (NPC) - bolus - intensity-modulated radiotherapy (IMRT)

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Introduction

Radiation therapy (RT) is the standard treatment of both the primary tumour and nodal metastases in nasopharyngeal carcinoma (NPC). As such adequate irradiation of the involved lymph nodes (LN) and at risk LNs is crucial for loco-regional control and survival. NPC has a higher incidence of cervical LN metastases compared to other head and neck cancers (Sham et al., 1990). LN metastases are seen in 60-90% of NPC cases (Chong et al., 1997; King et al., 2000; Ng et al., 2004; Glastonbury et al., 2007; Mao et al., 2008). A study in Penang General Hospital based on 285 patients treated from 2001-2005 revealed nodal involvement in 80.4% of the patients with 24.2% having N3a (6 cm or larger) (Phua et al., 2011). The presence of large cervical LNs represents a great challenge to the radiation therapist. With the advent of radiotherapy technique over the last few decades, most centers use megavoltage linac machines for RT which comes with skin-sparing ability. This skin-sparing effect has also been demonstrated with the latest RT technique with intensity-modulated radiotherapy (IMRT) (Price et al., 2006). However, with the presence of large cervical LNs this skin-sparing ability may not be desirable if the target volume extends to the skin. Gross nodal disease (GTV-N) requires a margin to form the clinical target volume (CTV-N) to account for microscopic spread. Moreover, with large LNs the chance of having extranodal extension is higher making it unjustifiable to reduce the margin for the CTV-N. Subsequently, the planning target volume (PTV-N) is obtained by adding another margin to the CTV-N to compensate for the effects of organ, tumour and patient movements, inaccuracies in beam and patient set-up (ICRU Report 50, 1993; ICRU Report 62, 1999). The PTV is a static, geometrical concept used for the treatment planning and for the specification of dose. It can be considered as a three dimensional envelope in which the tumour and any microscopic extensions reside and move within this envelope. For RT to be effective in achieving local control the PTV must be treated adequately. The exact margins to be used depend on the treating institution protocol. Our institution uses a 1 cm margin added to the

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GTV-N to form the CTV-N. Another 0.5 cm margin is added to the CTV-N to form the PTV-N.

IMRT is a radiation treatment technique with multiple beams incident from different directions in which at least some of the beams are intensity-modulated so that each beam intentionally delivers a non-uniform dose to the target. The desired dose distribution in the target is achieved after superimposing such beams. The additional degree of freedom to adjust intensities of individual rays are utilized to achieve a better target dose conformality and better sparing of critical structures (Chao et al., 2004). The technical advantages of IMRT over two-dimensional RT (2DRT) or three-dimensional conformal RT (3DCRT) have been well documented in the literature (Xia et al., 2000; Cheng et al., 2001; Hunt et al., 2001; Kam et al., 2003; Kristensen et al., 2007). More importantly, this has translated into improvement in clinical outcome in both early-stage and locally advanced disease. For early-stage disease the main advantage over 2DRT and 3DCRT is the reduction in acute and late complications which significantly affects the quality of life of long term survivors. This improvement is in the area of reduced severity of xerostomia (Kwong et al., 2004; Pow et al., 2006). For locally advanced disease the current standard of treatment is concurrent chemoirradiation based on the results of 2 meta-analyses involving 10 randomised control trials (Langendijk et al., 2004; Baujat et al., 2006). Though there has been no direct comparison of IMRT and 3DCRT in locally advanced NPC in a clinical trial, the results of IMRT in this setting has been very encouraging. Local control rate ranging from 87-96% at 2 years (Kwong et al., 2006; Lee et al., 2006; Wu et al., 2006) and 98-100% at 4 years has been reported in different studies (Lee et al., 2002; Sultanem et al., 2002). As such, our institution has recently adopted IMRT as the standard of treatment for our NPC patients.

For patients with large LNs it is our practice to include the skin as part of our PTV70-N if the GTV-N is very close to the skin. We do not adjust the PTV70-N so as to allow a 3-5 mm margin from the skin to the PTV70-N just so that the PTV70-N does not touch the skin or encroaches it. As the skin is not a critical organ at risk, we cannot see any justification to reduce margins required to form the CTV70-N and subsequently the PTV70-N as described earlier. When using bolus to treat large involved neck nodes, we have decided to call this the neck node bolus technique. We use a bolus of 1 cm thickness to ensure adequate coverage of the entire PTV. The usage of bolus in head and neck cancers has also been described in a study evaluating the rate of dermatitis using concurrent cetuximab and IMRT (Studer et al., 2011). In this study, the same principle was applied where the CTV was formed by adding a 1 cm margin around the GTV to account for microscopic spread. For grossly enlarged neck nodes not involving the skin the decision to use a bolus or not depended on its distance to the skin, positioning uncertainty of ≥3 mm and in accordance to the physicists' advice. When deemed necessary, they used a bolus of 1 cm to ensure adequate dose delivery to the skin close to the GTV. Our current study is done to compare the dosimetric coverage of the involved nodal target volumes with and without the use of bolus when treating our NPC patients with IMRT.

Materials and Methods

Patients

Data from 5 consecutive patients with NPC who were treated with bolus for large neck nodes using IMRT from November 2011-January 2012 in our institute were collected retrospectively for analysis. All these patients were treated radically with IMRT according to our institution's protocol. Re-planning with IMRT without bolus for these patients with exactly the same target volumes were done for comparison with the plans with bolus was performed.

IMRT planning

Patients were immobilized with a tailored beam directional shell in a comfortable neck position. Intravenous contrast-enhanced CT using 3 mm slice from the vertex to below the clavicles was performed using the CT simulator. CT data were imported to the Oncentra treatment planning system. Targets and organs at risk (OAR) were localized on the CT images. The gross tumour volume (GTV70) included all known gross disease in the primary area and the neck area determined from CT, MRI, clinical information and endoscopic examination. Enlarged neck nodes included any lymph nodes >1 cm or nodes with a necrotic center. The clinical target volume (CTV70) to account for microscopic spread was obtained by giving a margin of 1 cm circumferentially around the GTV. A second clinical target volume (CTV59.4) which is bigger than the CTV70 was delineated to account for all potential routes of spread for the primary and the nodal regions. These included the entire nasopharynx, parapharyngeal space, pterygopalatine fossa, posterior third of the nasal cavity and maxillary sinuses, inferior sphenoid sinus, posterior ethmoid sinus, base of skull (including the foramen ovale and rotundum bilaterally) and anterior half of the clivus. The cavernous sinus was also included for high risk patients. As for the nodal region, the CTV59.4 included the nodes in the junctional, parapharyngeal, retropharyngeal, submandibular regions, level II, III, IV, V nodes and supraclavicular fossa bilaterally. Subsequently, separate planning target volumes (PTV) were obtained by providing a margin of 0.5 cm around the CTV to account for variabilities of treatment set up and internal organ movement resulting in PTV70 and PTV59.4. Margins were reduced to as low as 1 mm for target volumes in close proximity to critical OARs i.e. the brainstem and spinal cord. The treating radiation oncologist modified these final PTVs accordingly based on the surrounding critical OARs. The contoured OARs included the spinal cord, brainstem, optic chiasm, optic nerves, eyes, lenses, cochlear, parotid glands, oral cavity, larynx, mandible, temporomandibular joints and brachial plexus. A bolus of 1 cm was used for any large neck nodes where the PTV70-N was at the skin or encroaches it. This bolus was placed on the thermoplastic beam directional shell over the location of the large LN. Dose calculation was done taking into account the presence of this bolus.

Table 1. Dosimetry Results of 5 Patients with and without Bolus

Patient	Size (XxYxZ) (cm)	Distance of GTV-N to skin (cm)	V70 of PTV70-N (%)		V66.5 of PTV70-N (%)		V65.1 of PTV70-N		Surface dose of PTV70-N Gy (%)	
			With bolus	Without bolus	With bolus	Without bolus	With bolus	Without bolus	With bolus	Without bolus
1	3.2x3.6x3.6	0.8	88.1	85.0	95.6	91.9	96.6	93.3	52.0 (74.3)	21.9 (31.3)
2	3.0x5.3x4.3	0.4	99.3	87.5	99.9	91.5	100	92.6	66.7 (95.3)	23.9 (34.1)
3	2.8x4.5x3.6	0.4	87.9	79.8	93.3	87.6	94.4	89.2	55.5 (79.3)	24.2 (34.6)
4	2.8x3.0x4.2	0.4	91.0	79.6	97.3	87.1	99.1	88.7	66.1 (94.4)	26.5 (37.9)
5	1.5x1.9x2.0	0.8	95.6	76.0	98.8	86.3	97.9	88.6	65.4 (93.4)	21.0 (30.0)
Mean			92.4	81.6	97.0	88.9	97.6	90.5	61.1 (87.3)	23.5 (33.6)

Inverse planning for IMRT was performed using the CMS XiO version 4.60. The prescribed doses were 70 Gy to the PTV70 in 33 fractions at 2.12 Gy per fraction and 59.4 Gy in 33 fractions to the PTV59.4 at 1.8 Gy per fraction. With regards to the OARs, the critical organs were the spinal cord and brainstem. Maximal allowable dose to any part of the spinal cord was 45 Gy and for the brainstem it was 54 Gy without any compromise. The optic nerves and eyes were kept below 50 Gy while the optic chiasm was kept below 54 Gy. If the doses of any of these optic apparatus were exceeded due to extensive disease informed consent for blindness was obtained from the patient prior to plan approval. The maximal allowable dose for the brachial plexus was 66 Gy unless there was gross disease in its vicinity. Dose Volume Histogram (DVH) was generated for all the target volumes and OARs. For evaluation DVH, the treating oncologist used the following guideline for acceptability of a plan: 95% of any PTV70 was at or above 70 Gy and 99% of PTV70 was at or above 65.1 Gy. In addition, no more than 20% of the PTV70 was at or above 77 Gy and no more than 5% of the PTV70 was at or above 80 Gy. Plans fulfilling the criteria for PTV70 needed to be within the dose constraints for OARs as outlined above. Quality assurance for the finalized plan was done using the MapCHECK tool for point dose and fluence testing. Verification of isocentre was subsequently done by checking orthogonal fields using the SimViewNT Siemens Simulator. IMRT was delivered via seven fixed angles with an Elekta Precise Linear Accelerator. Portal imaging was done weekly using the Elekta iview electronic portal imaging version 3.4. Aceptable overall treatment time (OTT) was set at 7 weeks. Treatment was delivered once daily, 5 fractions per week, over 6 weeks and 3 days. All targets were treated simultaneously.

Comparison of target coverage with and without bolus

For each of the 5 patients, DVHs were generated for both the IMRT plans with and without bolus using a total dose of 70 Gy. The measures used to compare the dosimetry of nodal volume coverage between treatment with bolus and without bolus were the V70 for PTV70-N which is the percentage volume of the target receiving 70 Gy or more, V66.5 for PTV70-N which is the percentage volume of the target receiving at least 95% of the prescribed dose (70 Gy), V65.1 for PTV70-N which is the percentage volume of the target receiving at least 93% of the prescribed dose and the surface dose of the PTV70-N. The means of the comparison measures listed above were obtained for both plans with bolus and without bolus.

Results

All 5 patients completed their IMRT treatment with 1cm bolus over the enlarged nodal region within the stipulated 7 weeks OTT. All 5 patients were also treated with weekly concurrent intravenous cisplatinum 30 mg/m^2. Only 1 patient experienced grade 3 skin reaction (confluent, moist desquamation) with 2 patients having grade 2 skin reaction (patchy moist desquamation) and 2 patients had grade 1 skin reaction (dry desquamation). All patients had complete recovery of the skin reaction 6 weeks post IMRT. The mean size of the largest diameter of the enlarged lymph nodes for the 5 patients was 3.9 cm. The dosimetry results of the comparison for the PTV70-N with the use of bolus and without bolus are found on Table 1. The mean distance of the GTV-N to the skin surface is 0.6 cm. This study showed obvious superiority of using bolus with IMRT over non bolus plans with IMRT when treating patients with enlarged lymph nodes. The mean V70 of PTV70-N for the 5 patients showed an absolute advantage of 10.8% (92.4% vs. 81.6%) while the V66.5 of PTV70-N had an advantage of 8.1% (97.0% vs. 88.9%). The mean V65.1 of PTV70-N also showed an advantage of 7.1% (97.6% vs. 90.5%). The mean surface dose for the PTV70-N was also much higher at 61.1 Gy for the plans with bolus compared to only 23.5 Gy for the plans without bolus.

Discussion

This study clearly shows the superiority of using a bolus in the treatment of NPC with IMRT when patients have lymph node involvement. In fact, there might be an argument that a thicker bolus should had been used to achieve an even better dosimetry with regards to the PTV70-N coverage. Our patients had a mean coverage of 92.4% for the V70 of PTV70-N for which it was slightly less than ideal where our institution's protocol called for coverage of at least 95% for this measure. The V65.1 which is 93% of the prescribed dose was superior with the bolus plan at 97.6% which ideally should be above 99%. The V66.5 for PTV70-N also fared much better with a mean coverage of 97.0%. Plans without bolus were totally unacceptable with a mean of only 81.6% for the V70 of PTV70-N, 88.9% for the V66.5 and 90.5% for the V65.1. A bolus of 1 cm was used when treating our patients and this study actually shows that this might be inadequate. In addition, the mean surface dose of the PTV70-N was very low for the plans without bolus at only 23.5 Gy. We can see no justification for the treatment of NPC with nodal

involvement without the use of bolus over the involved nodal region.

The mean distance of the closest part of the GTV-N to the skin surface was approximately 0.6 cm. There can be no justification for not giving a margin to form the CTV70-N. In our institution a margin of 1 cm is used. The literature clearly shows that enlarged lymph nodes are at high risk of having extra-capsular extension (ECE). This risk is as high as 53-83% for nodes of 1-3 cm and 74-95% for nodes above 3 cm (Annyas et al., 1979; Johnson et al., 1981; Carter et al., 1987; Hirabayashi et al., 1991). In fact, a margin of 2 cm was initially proposed by Chao and colleagues in their sentinel paper on delineation of nodal target volume for head and neck cancers when IMRT was in its infancy to prevent geographical miss (Chao et al., 2002). A later study on the same subject recommended a margin of at least 1 cm from the GTV-N to form the CTV70-N for enlarged lymph nodes smaller than 3 cm based on assessment of microscopic tumour extension beyond cervical lymph node capsules from 96 dissected lymph nodes from 48 patients (Apisarnthanarax et al., 2006). Thus, even without accounting for organ movement and set up error, the margin required for microscopic spread itself will bring the PTV70-N to the skin surface. As most involved lymph nodes are very close to the skin surface, we feel strongly that the CTV70-N cannot be compromised just to spare the skin. Margin for organ movement and set-up error varies from centre to centre and in our centre a margin of 0.5 cm is used. In the head and neck region with the use of beam directional shell, organ or target movement can be kept to a minimum. However, there can be no compromising on the possibility of set-up error. This is a margin that needs to be given even in the best of centers as to err is human. We would argue that if the CTV70-N is already at the skin surface then the PTV70-N has to be extended beyond the skin onto the bolus to account for set-up error. This will make the thickness of the bolus required even thicker. Thus, we need to be very careful not to clip the PTV70-N from the skin surface in order to reduce skin reaction.

A recent study conducted in our center revealed a worryingly low 5 years overall survival of only 33.3% before the use of IMRT (Phua et al., 2011). As we move towards newer treatment technique we must get our priorities right. IMRT has often been touted as a technique that can maintain good treatment outcome while reducing treatment toxicities especially with regards to xerostomia. However, we are cognizant to the fact that we must strive for better treatment outcome in view of the past poor treatment result in our center and this can only be achieved by sticking closely to the fundamentals of radiotherapy. There can be no compromise of margins especially with regards to reducing toxicity to non vital organs. In this study, the use of bolus of 1 cm did not cause undue harm to the patient. All patients had complete recovery of their skin toxicity 6 weeks post treatment. Studies have estimated a loss of approximately 1.4% local control for every day of delay beyond the overall treatment time (OTT). This will translate to a loss of 10-12% of local control with a delay of one week during treatment (Maciejewski et al., 1983; Vikram et al., 1985; Maciejewski et al., 1989; Fowler et al., 1992). This study shows that the use of bolus for enlarged neck nodes will not compromise the treatment OTT. In fact, all 5 patients completed their treatment within 6.5 weeks. As such we need not worry about using a bolus when treating patients with IMRT for NPC. Though we need to be wary of acute skin reaction during treatment, patients should be able to complete their treatment within the stipulated OTT of 7 weeks.

We feel that the concern for skin toxicity with radiotherapy is overstated. Firstly, we are suggesting for bolus to be used over the enlarged lymph node region and not the entire neck. A 50% risk in 5 years of sustaining a grade 4 skin toxicity resulting in ulceration has been estimated to require a dose in excess of 70 Gy over an area larger than 100 cm^2 (Emami et al., 1991). In our experience when using bolus to treat enlarged lymph nodes, skin toxicity has not been a major problem. Simple measures such as advice on gentle washing, keeping the area clean and dry, avoiding collared shirts and scratching and medications for itch and pain if required can deal with the majority of skin reactions. For wet desquamation we have been using topical flavine solution after gentle washing and drying.

Anecdotal evidence from our experiences and observations show that oncologists/physicists either seldom or never use a bolus when treating NPC with nodal involvement. This occurs with treatment using either conventional, 3D conformal radiotherapy or IMRT. This may stem from the fear of skin toxicity or teaching in the field of radiotherapy during their training period. We feel very strongly that the neck node bolus technique is a must in significantly enlarged nodes to ensure that the nodal disease is treated adequately and the thickness of the bolus required should be adjusted according to the dosimetry of the treatment plan.

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