RESEARCH ARTICLE

Plan Dose Evaluation of Three Dimensional Conformal Radiotherapy Planning (3D-CRT) of Nasopharyngeal Carcinoma (NPC): Experience of a Tertiary Care University Hospital in Pakistan

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Abstract

Background: Radiation therapy is the mainstay of treatment for nasopharyngeal carcinoma. Importance of tumor coverage and challenges posed by its unique and critical location are well evident. Therefore we aimed to evaluate our radiation treatment plan through dose volume histograms (DVHs) to find planning target volume (PTV) dose coverage and factors affecting it. Materials and Methods: This retrospective study covered 45 histologically proven nasopharyngeal cancer patients who were treated with definitive 3D-CRT and chemotherapy between Feb 2006 to March 2013 at the Department of Oncology, Section Radiation Oncology ,Aga Khan University Hospital, Karachi, Pakistan. DVH was evaluated to find numbers of shrinking field (phases), PTV volume in different phases and its coverage by the 95% isodose lines, along with influencing factors. Results: There were 36 males (80%) and 9 females (20%) in the age range of 12-84 years. Stage IVA (46.7%) was the most common stage followed by stage III (31.1). Eighty six point six-percent received induction, 95.5% received concurrent and 22.2% received adjuvant chemotherapy. The prescribed median radiation dose was 70Gy to primary, 60Gy to clinically positive neck nodes and 50Gy to clinically negative neck regions. Mean dose to spinal cord was 44.2Gy and to optic chiasma was 52Gy. Thirty seven point eight-percent patients completed their treatment in three phases while 62.2% required four to five phases. Mean volume for PTV3 was 247.8 cm^3 (50-644.3), PTV4 173.8 cm^3 (26.5-345.1) and PTV5 119.6 cm^3 (18.9-246.1) and PTV volume coverage by 95% isodose lines were 74.4%, 85.7% and 100% respectively. Advanced T stage, intracranial extension and tumor volume >200 cm^3 were found to be important factors associated with decreased PTV coverage by 95% isodose line. Conclusions: 3D CRT results in adequate PTV dose coverage by 95% isodose line. However advanced T stage, intracranial extension and large target volume require more advanced techniques like IMRT for appropriate PTV coverage.

Keywords: Three dimensional conformal radiotherapy (3D-CRT) - nasopharyngeal carcinoma - plan dose evaluation

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Introduction

Nasopharyngeal carcinoma (NPC) is a disease with distinct ethnic and geographic distribution as compare to other head and neck cancer (Jemal et al., 2010). The majority of newly diagnosed NPC patients have loco-regionally advanced disease (Abbasi et al., 2011). Traditionally Nasopharyngeal carcinoma has been treated with definitive chemo-radiotherapy due to its unique location (Baujat et al., 2006). Very little help is available from surgical side in its management except salvage neck dissection or biopsy (Chen et al., 2012). The basic aim of treatment is to deliver a curative dose of radiotherapy to the tumor without damaging the surrounding normal structures. To achieve or target this aim put the radiation oncologist into very challenging situation due to its strategic location and proximity to normal critical structure like brain stem, visual apparatus and spinal cord. Moreover this issue is complicated by the fact that the radiation dose required to eradicate tumor from nasopharynx are far more than what is considered to be the tolerance limit of surrounding normal structures (Liu et al., 2003). To address these challenges 2 dimensional radiotherapy techniques, that has been used traditionally, was replaced by three dimensional conformal radiotherapy (3DCRT) (Teo et al., 2004). CT scan based planning provides better delineation of tumor target and organ at risk with clearer radiologic visualization of their spatial relation, more optimization of beam orientation, beam weighting and beam shaping through beam eye view application (BEV)

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thus improving the therapeutic index. It represents a major step forward in modern treatment planning. However the problem of dose inhomogenity and suboptimal coverage is still unresolved because of highly infiltrative growth pattern with a propensity to spread through skull base foramina to the intracranial structures particularly visual apparatus as well as parapharyngeal space and large neck lymph nodes, in addition, there is a variation of the anatomic structure of the nasopharynx between individuals (Kam et al., 2003). This has led the radiation oncologist to break the treatment plan into different phases that has also compromised tumor coverage. Importance of tumor volume also emphasized by the recent studies that shows tumor volume to be important prognostic factor in term of local control and diseases free survival therefore good tumor coverage according to the international commission on radiation units and measurement (ICRU) report 50 recommendation, got further importance (Sarisahin et al., 2010). By taking into consideration all these facts we conducted a study that retrospectively evaluate the PTV coverage by the three dimensional conformal radiotherapy at a single institution. Since failure at the primary site is the major fear due to limited surgical or other treatment support as compared to the nodal site, secondly coverage of the nodal area required electron beam therapy as well and its contribution in the dose coverage is not evaluated through dose volume histogram in our present planning system therefore we focus on the treatment plans for the primary tumor target volume only in the our study. Results obtained are compared with recent literature.

Materials and Methods

Patient cohort

A retrospective review was conducted on case records of all NPC patients treated at Department of Oncology section Radiation Oncology Aga Khan University Hospital Karachi Pakistan with three dimensional conformal radiotherapy from February 2006 to March 2013. We included all patients with newly diagnosed, non metastatic histologically proven diseases who were fit enough to tolerate a course of definitive chemo-radiotherapy.

All patients were staged by a standard protocol comprising physical examination, fiber-optic nasopharynogoscopy, chest radiograph, liver ultrasound and a radionuclide bone scan was done where indicated. CT scan head and neck was done in all patients along with MRI Head in patients who were found to have intracranial extension. All patients were staged according to the international Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) 2009 staging system.

Radiation treatment

All patients underwent simulation after immobilization in supine position with a thermoplastic mask. Area of interest defined and parameters were taken after which CT scan was performed with IV contrast using 3-5mm slices from the head to the level of 2cm below the sternoclavicular joint sometimes up to the level of carina in patients who had enlarged Supraclavicular lymph nodes. The images were transferred to the treatment planning system Varian eclipse for tumor marking and planning. The planning target volume was marked according to the international Commission on Radiation Units and Measurement (ICRU) report 50 and 62. The gross tumor was marked based on the pre-chemotherapy scan in patients who received neo-adjuvant chemotherapy; a margin of 15-20 mm was added to make it clinical target volume (CTV) and finally 3-5 mm margin to make it planning target volume (PTV). Typically a radiation dose of 70Gy was delivered to the primary target volume with curative intent, 60-66Gy to all grossly involved lymph nodes and a minimum of 50Gy to all nodal region that were at risk of harboring microscopic diseases. Treatment was given in once daily fraction @2Gy per fraction five days a week except in one patient who got radiation @2.2Gy per fraction due to the treatment interruption. Dose was prescribed at 100% isodose line. A dose variation of +7 to -5% was accepted according to the ICRU report 50 recommendation. Dose was calculated using eclipse software with full 3D compensation and heterogeneity corrections. Patients were treated with 6MV photon beam initially followed by an 18MV photon boost to the primary. The treatment was delivered by Varian linear accelerator 2100C with 120 multileaf collimators. During treatment portal images conventional or electronic were obtained and compared with planning images for verification.

As already discussed in the introduction that radiotherapy dose required to cure the NPC cancer is greater than the tolerance of surrounding normal structure therefore treatment is divided into phases. Typically in phase 1 lateral parallel opposed field approach were used that extend 1cm superior to the cranial extent of NPC tumor to the as low as reasonably possible by keeping the fact of shoulder clearance in lateral fields. It includes primary tumor and the cervical nodes up to 40Gy along with shielding for posterior cranial fossa, oral cavity and eyes. In phase 2 the posterior border of lateral fields moved anteriorly to shield the spinal cord and delivered the dose up to 50Gy with electrons beam. In Phase 3 field shaping was done by keeping two things in mind first status of the lymph nodes whether it were enlarged at initial diagnosis so that it boosted up to 60-66Gy with electron. Secondly, boost to the primary target volume that had minimal intracranial extension or skull base involvement so that optic chiasm shielding was introduced at 50Gy and delivered dose up to 66-70Gy. However there were situation where primary diseases was so extensive either in the form of intracranial extension or surrounding structure involvement that we have to reduced our target volume so that normal structure tolerance dose were not exceeded and introduced phase 4 or in some case up to phase 5 that focused only primary target volume or epicenter of tumor. The lower neck nodes were treated to 50-66Gy with either a direct anterior field or anterior-posterior opposed fields junctioned to the superior lateral fields with midline shielding to protect the spinal cord once its tolerance dose reached through mono-isocenter technique.

In patients who had intracranial extension or tumor involving the orbit or frontal sinus split field technique were used. Tumor with anterior extension to the nasal cavity anterior field was introduced after phase 2. PTV 4-5 usually covered by 3-4 field (oblique, anterior, lateral).

Chemotherapy

All patients in the study group received chemotherapy either in the neo-adjuvant, concurrent or adjuvant setting. Chemotherapy regimen was based on cisplatin and fluoropyrimidine (5-FU).

Methods

Medical charts were reviewed to obtain demographic and treatment information. For technical purpose cumulative dose volume histogram (DVH) of each plan was evaluated to find the number of phases required to complete the treatment, volumes of different phases as well as its coverage by the 95% isodoses line. The reason to choose 95% isodose line for PTV coverage was as it represents the minimal acceptable isodose limit of the dose delivered to a well defined prescription point within the target according to ICRU report 50 recommendation. Dose to the critical normal structures were also noted. When 95% isodose line failed to cover the PTV, efforts were made to determine the factors responsible for it.

Data was entered and analyzed through SPSS (Statistical Package for Social Sciences) version 19. Descriptive statistics were used to summarize data.

Results

In the study cohort there were 36 (80%) male and 9 (20%) female. Median age at presentation was 41 years ranged from 12-84 years. No patient with T1 diseases was identified, 10 (22.2%) had T2 diseases while 12 (26.7%) and 23 (51.1%) had T3 and T4 diseases respectively. Majority of the patients had N2 diseases 24 (53.3%) while only one patient was found to have no neck node diseases. Most of the patients had locally advanced diseases at presentation especially stage IV A&B (46.7% and 11.1%) respectively with 33.3% had diseases that extend intracranially at presentation (Table 1). Median radiation dose was 70Gy. The lowest dose in the cohort was 60Gy that was prescribed to a 12 years old boy according to accompanied pediatric protocol. Other than that 66Gy was the minimum prescribed dose except two cases one had extensive intracranial extension and tolerance limit to surrounding structure was reached at 64Gy other was planned for 70Gy but he refused for further treatment after 64Gy. Almost all patients received chemotherapy. Neo-adjuvant chemotherapy was offered to 39 (86.6%) who had locally advanced diseases at presentation. Adjuvant chemotherapy was offered to 10 patients who had residual diseases at the end of the treatment. Fifty-percent of the patients completed their treatment in 4 phases. While 37% patients were finished their treatment in 3 phases. However in 5 patients phase 5 were used to achieve prescribed doses. Planning target volume showed reduction in the volume as it went up from PTV 3 to PTV 5 due to shrinkage of fields as well as volume (Table 2).

PTV coverage by 95% isodose line was worst for PTV 3 due to its large volume and best for PTV 5 as its only include the epicenter of the diseases i.e. nasopharynx. Radiation dose to the critical surrounding structure were also within tolerance limit. No effort had been made to limit the dose of parotid glands as majority

Table 1. Characteristics of Patients with Nasopharyngeal Carcinoma

Characteristic		No. of patients (%)
Gender	Male	36 (80%)
	Female	9 (20%)
Age Median (range) years		41 (12-84)
T category	T1	0 (0%)
	T2	10 (22.2%)
	T3	12 (26.7%)
	T4	23 (51.1%)
N Category	N0	1 (2.2%)
	N1	15 (33.3%)
	N2	24 (53.3%)
	N3	5 (11.1%)
Stage	I	0 (0%)
	II	5 (11.1%)
	III	14 (31.1%)
	IV A	21 (46.7%)
	IV B	5 (11.1%)
Intracranial Extension		15/45 (33.3%)

Table 2. Specifications of Radiation Treatment

Treatment specifications		No. of patients (%)	
Radiation dose median (Range)		70 Gy	(60-74 Gy)
Chemotherapy		N=45	(%)
	Neo-adjuvant	39	(86.6%)
	Concurrent	43	(95.5%)
	Adjuvant	10	(22.2%)
Radiation therapy phases	3	17	(37.8%)
	4	23	(51.1%)
	5	5	(11.1%)
Planning Target Volume (PTV)		Mean (Range)in cm^3	
	3	247.8	(50-644.3)
	4	173.8	(26.5-345.1)
	5	119.6	(18.9-246.1)
PTV coverage by 95% isodose line		Observed/total (%)	
	3	29/39	(74.4%)
	4	24/28	(85.7%)
	5	5/5	(100%)
Radiation dose to spinal cord: Mean (range)		44.2	(42-46.4 Gy)
Radiation dose to optic chiasm: Mean (range)		52	(47.5-56.5 Gy)

Table 3. Percent of Cases with PTV Undercoverage by 95% Isodoses by T Stage

PTV	T stage				
	T1 (%)	T2 (%)	T3 (%)	T4 (%)	Total (%)
PTV 3	-	2 (20)	2 (20)	6 (60)	10 (100)
PTV 4	-	-	1 (25)	3 (75)	4 (100)

Table 4. Distribution of PTV Under Coverage by 95% Isodose Line According to the Intracranial Extension and Tumor Volume

PTV	Intracranial extension		
	Yes (%)	No (%)	Total (%)
PTV 3	5 (50)	5 (50)	10 (100)
TV 4	3 (75%)	1 (25)	4 (100)
PTV	Tumor volume		
	<200cm^3 (%)	>200cm^3 (%)	Total (%)
PTV3	3 (30)	7 (70)	10 (100)
PTV4	0	4 (100)	4 (100)

of the patients presented with advanced diseases with parapharyngeal involvement and enlarged bilateral cervical lymphadenopathy (Table 3).

PTV under coverage by 95% isodose line were stratified with T stage, volume of PTV and found that it was progressively deteriorated as the T stage got advanced especially with intracranial extension and when PTV volume exceed 200 cm^3 (Table 4).

Discussion

Nasopharyngeal carcinoma posed a unique challenge to the radiation oncologist for its management due to its crucial location, infiltrative spread pattern, advanced stage at presentation and surrounding critical normal structure. Local control remains a major problem for many patients and it is directly related to the dose delivered to the target volume (Teo et al., 2006). Although classical Ho's 2D technique for nasopharyngeal cancer had been traditionally practiced for a long time but attempts of dose escalation and introduction of CT scan based planning system led to the realization of 2D technique limitation. This was addressed by Waldron et al. (2003) in his paper in which he transferred the 2D fields of the treated patients to 3D planning system and then it was evaluated in term of 53, 90 and 95% isodoses line coverage of GTV and area of under coverage was also determined. The GTV was covered by the 50, 90 and 95% isodoses lines of all phases of the multiphase plan in only 50, 20 and 9% of patients respectively. The area of under coverage was found to be superior (base of skull) followed by posterior/superior or posterior (brainstem/spinal cord) (Waldron et al., 2003). Chau et al. (2001) also did the 3D dosimetric evaluation of the conventional radiotherapy technique found that problem of geographical miss was less significant in early stage diseases and the area with highest potential for missing include edge of shielding, blocks and field border (Chau et al., 2001). One of the interesting and important differences between 2D and 3D techniques is the pattern of failure 2D results in loco regional failure while three dimensional results in failure at distant site due to improved local control (Teo et al., 2004).

Three dimensional radiotherapy is the current standard of practice, it provides improvement in dose distribution conformity to the tumor volume while concomitantly reducing dose to the surrounding normal structure, generally it is based on CT scan however others imaging modalities like MRI, PET is also emerging for planning purpose (Nishioka et al., 2002). CT scan based voluming although provide good information of tumor extent but due to less sensitivity for soft tissue sometimes result in over estimation leading to large volume that is difficult to cover with high dose due to surrounding normal structure (Rasch et al., 2010).

Although 3D-CRT results in improved tumor coverage but it has its own limitations like planner's expertise, manual iteration to achieve an optimal plan and more important its ability to control the radiation beam in two dimensions only. Also the stage and shape of the tumor has found to have significant influence as multidirectional spread lead to irregular shaped volume particularly concave shape that is very difficult to be looked after by 3 dimensional radiotherapy. Studies have shown that as the tumor stage advances especially intracranial extension tumor coverage become compromised as we have also observed in our study as well, being a developing country majority of the patients presented with advanced stage due to lack of awareness and scarce medical facilities as shown in our previous study (Abbasi et al., 2011). Secondly due to its unique location advanced stage at presentation is common as evident by study from India by Sharma et al. (2011) who reported that almost 71.5% of patients had advanced diseases at presentation and 25% had intracranial extension (Sharma et al., 2011). Moreover small separation between critical structures and target also create trouble for tumor coverage. All these factors were identified by Lee et al. (2002). To address these challenges more advanced technology were developed like intensity modulated radiotherapy (IMRT) and compared it with 3DCRT. Various studies both case series as well as randomized trials have been published on its merits and demerits (Bhide et al., 2012). The potential of IMRT for better tumor coverage especially for concave tumor volume has been demonstrated in nasopharyngeal cancer patients (Tribius et al., 2011). In a series of 23 patients of nasopharyngeal cancer treated with IMRT, Hunt et al. (2001) compared IMRT treatment plan with 2DRT and 3DRT. They found that IMRT resulted in an escalation of the mean target (PTV) dose to 77.3Gy as compared to 67.9Gy from conventional plan and 74.6Gy from 3D plan. Also produced improved dose coverage of the skull base and cervical nodes and a significant dose reduction to spinal cord, temporal lobe and mandible. Reduction of spinal cord dose from 49Gy (2D) to 44Gy and 34.5Gy from 3D and IMRT respectively. Moreover volume of mandible and temporal lobes getting more than 60Gy also decreased by 10-15% with IMRT (Hunt et al., 2001). This finding were confirmed by Chang et al. (2011) who compared two different techniques of IMRT (fixed field and serial tomotherapy) with conventional 3DRT in 12 patients and found that IMRT resulted in better CTV and GTV coverage for the primary tumor and neck nodes (Chung et al., 2011). Another study by Hsiung et al. (2002) compared the IMRT and 3D-CRT plan for the boost treatment of new onset nasopharyngeal cancer or as salvage he observed a more homogenous dose distribution in IMRT plan he found the mean target dose D05 (dose to 5% volume) was decreased from 127.9% with 5-fields 3D-CRT to 117.4% with 5-fields IMRT ($p=0.001$ compared with 3D-CRT) and to 112.7% with 7-fields IMRT ($p<0.001$ compared with 3D-CRT). He also identified five anatomic factors that were associated with tumor coverage compromise from 3D-CRT and got maximum benefit with IMRT. These were >7cm vertical length of target, minimal distance between target and brainstem <0.1cm, anterior-posterior (AP) overlap of target and brainstem >0.6cm, maximal AP overlap of target and spinal cord and vertical overlap of target and eye (Hsiung et al., 2002). Investigator from Hong Kong also reviewed the literature and found better tumor coverage, geometric accuracy, dosimetric homogeneity and normal organ sparing and allows room for dose escalation in locoregionally advanced nasopharyngeal cancer with IMRT (Teo et al., 2004).

Importance of tumor volume has been established in others head and neck cancer but its role in nasopharyngeal cancer is not cleared although studies have shown a direct relationship between tumor volume and outcome (Guo et al., 2012). According to studies tumor volume indicated the number of tumor clonogens that should be removed. An increasing tumor bulk relates to an increasing number of tumor clonogen requiring sterilization by higher radiation dose (Ogawa et al., 2013). Though nasopharynx tumor staging system is based on tumor extent to surrounding structure, several studies have shown that tumor volume varied substantially within the same T group hence effecting tumor coverage by the radiation isodoses therefore establishing as a prognostic significance (Zhou et al., 2007). We also witnessed the same observation in our study that if tumor volume was <200cm^3 then it was better covered by 95% isodoses line as compared to tumor volume of >200cm^3.

With the realization of the limitation of the our study i.e. retrospective and small cohort of patients it shows the limitation of the standard conformal therapy to adequately provide coverage of the planning target volume in complex cases with advanced surrounding structure invasion especially intracranial extension and large volume. Our practice also evolved considerably over this period with incorporation of field in field and split field techniques to improve tumor coverage without harming adjacent normal structure and now incorporating IMRT system for such complicated cases.

In conclusion, 3D conformal radiotherapy result in good tumor coverage by 95% isodose line in majority of nasopharyngeal cancer but struggle with its limitation when come across with advanced stage tumor, intracranial extension and large tumor volume. Therefore more advanced technique is required for such complex cases to improve outcome.

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