Comparative Study between Intensity Modulated Radiotherapy and Conventional Radiotherapy in Treatment of non Metastatic Squamous Cell Carcinoma of the Nasopharynx

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Abstract:

Background: Carcinoma of the nasopharynx is one of the most common cancers in the head and neck areas. Control of the disease at an early stage with radiotherapy alone is usually successful. However, in loco regionally advanced disease, concurrent chemo radiotherapy is the standard treatment

As regards the conventional 2dimensional radiotherapy, many studies have shown equivalent results to intensity modulated radiotherapy on the level of local, regional and distant disease control while others have reported that intensity modulated radiotherapy has improved both the overall survival and local disease control and decreased late toxicities compared to the conventional 2 dimensional radiotherapy.

The aim of the study: Is to compare between intensity modulated radiotherapy and conventional 2D radiotherapy on the level of treatment outcome and treatment related morbidities in patients with non metastatic squamous cell carcinoma of the nasopharynx.

Patients and methods: Patients treated by radiotherapy +/- chemotherapy from January 2013 to January 2023 in Sohag University Hospital were retrospectively enrolled and analyzed.

Results: Forty one patients were identified. Twenty one (51%) were treated with intensity modulated radiotherapy while 20 (49%) were treated with conventional 2D radiotherapy. Chemotherapy was given in 33 cases (80%). No significant differences were noticed between both arms on the level of acute and chronic treatment related toxicities.

The 5-y overall survival (OS), local progression free survival (LPFS) and distant progression free survival (DPFS) with conventional 2D radiotherapy and intensity modulated radiotherapy in the whole cohort were 72% versus 64%; p = 0.218 & 63% versus 85%; p = 0.220 and 77% versus 88%; p = 0.449 respectively. In univariate analysis, many significant findings were evident. Age > 51 y was associated with poorer OS in the whole cohort (p = 0.049) and also in the subgroup received chemotherapy (p = 0.047). Intensity modulated radiotherapy has significantly improved the 5-y DPFS in stage II disease (p=0.049). Chemotherapy significantly improved LPFS in advanced stages (p=0.012). Irradiation dose at 70 Gy has demonstrated significantly better OS and LPFS in advanced versus early stage (p = 0.041 and 0.012 respectively) and lastly male patients have shown significantly lower OS (p=0.041) compared to females in the older subgroup of patients. In multivariate analysis, younger age was associated with significantly better 5-y OS versus older age in the subgroup received concurrent chemo radiotherapy (HR: 0.123; 95% CI: 0.021 – 0.712 & p = 0.019).

Conclusions: Although this retrospective study has enrolled a small number of patients, we conclude that in early stage of cancer nasopharynx, intensity modulated radiotherapy alone is successful and preferable than conventional radiotherapy while in advanced stages both chemotherapy (preferably, both induction and concurrent) and high dose radiation therapy should be considered. Younger ages associated with better survival outcome and, more studies are needed to improve the outcome in elderly male patients.

Key words: Intensity modulated radiotherapy, conventional radiotherapy, carcinoma of the nasopharynx

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Introduction:

Carcinoma of the nasopharynx is one of the most common cancers in the head and neck areas. Males are two to three times more likely to have it than females. The peak age of incidence is between 50 and 60 y [1]. It is strongly associated with the Epstein-Barr virus [2]. It is endemic in Southeast Asia with incidence rates from 15 to 50 per 100 000 with an intermediate incidence in North Africa and Far Northern hemisphere while in the West it occurs sporadically. In Egypt where cigarette and water pipe smoking rates have recently increased the incidence rate is about 3.4% at age between 50 and 54 y [3]. Owing to the radio sensitivity of the tumor and the deep seated location of the nasopharynx, radiotherapy has been established as the primary modality of treatment since the 1950s [4, 5] and control of the disease at an early stage with radiotherapy alone is usually successful [6]. However, in loco regionally advanced disease, concurrent chemo radiotherapy (CCRT) is the standard treatment [7]. In the past, before the era of conformal radiotherapy head-neck cancers were treated with conventional irradiation techniques without major emphasis on shielding normal tissues [8] resulting in considerable acute and late morbidities [9,10], most commonly, radiation-induced xerostomia and dry mouth due to salivary glands hypofunction leading to difficulty in speech and swallowing [10,11]

Over the years, technological advancement in treatment planning based on three-dimensional computed tomographic imaging have led to more precise conformation [8] of radiation dose to the target organs at the same time, avoiding much damage to adjacent organs at risk (OARs). Intensity modulated radiation therapy (IMRT) has emerged as an advanced form of high-precision conformal technique using non uniform beam intensities determined through computer based optimization to achieve the desired dose distribution [12]. It can dosimetrically spare normal tissues to a greater extent than 2D Rth, however, whether or not this advantage can be translated into clinical effectiveness without compromising tumor control remains a question in radiation oncology community [13].

Systematic reviews have been made to compare the effectiveness of IMRT and conventional two dimensional radiotherapy (2D Rth) in terms of oncologic outcomes [13,14], xerostomia and quality of life [15, 16, 17].

A systematic review and meta analysis conducted by Jayson et al showed that there is a benefit across all stages with IMRT compared to 2D Rth in terms of oncologic outcomes. However, upon stratification, it was only evident in T4, N2, and stage III disease on the level of the 5-yr local control, regional-nodal control, and overall survival (OS). Also they have found that physician-graded xerostomia was consistently better in the IMRT arm compared to the 2D Rth arm [13].

Taifeng and colleagues in their meta analysis have found that IMRT was associated with higher 5-year OS (OR = 1.70; 95% CI = 1.36–2.12), local recurrence free survival (LRFS) with an odds ratio (OR = 2.08; 95% CI = 1.82–2.37), and progression free survival (PFS) with an odds ratio (OR = 1.40; 95% CI = 1.26–1.56). Additionally, the incidence of late toxicities such as late xerostomia, trismus and temporal lobe neuropathy (TLN) in IMRT group were significantly lower than with 2D Rth with Odd ratios at 0.21; 95% CI = 0.09–0.51 & 0.16; 95% CI = 0.04–0.60 and 0.40; 95% CI = 0.24–0.67 respectively [18].

On the other hand, other researchers have reported no significant advantage for IMRT over 2D Rth in treatment outcome. OuYang and colleagues in a retrospective study included 1198 patients reported that IMRT obtained 5-yr OS (91.3% vs 87.1%, p = 0.120), loco-regional relapse free survival (LRFS) (92.3% vs 90.4%, p = 0.221) and distant metastasis-free survival (DMFS) (92.9% vs 92.1%, p = 0.901) rates comparable to 2D Rth [19].

Marta and colleagues in a systematic review included 871 head and neck cancer patients, (82% of them with cancer nasopharynx) have reported similar loco-regional control and OS between IMRT and 2D Rth but, with significant benefit regarding xerostomia grade 2–4 (Hazard ratio; HR = 0.76; 95% CI: 0.66, 0.87; p < 0.0001) in favor of IMRT [14].

Zhang Y and colleagues in a retrospective study that enrolled 190 patients treated with IMRT and 190 treated with 2D Rth demonstrated that IMRT was superior to 2D Rth in term of the 4-year loco-regional control rate and the relapse-free survival rate without reducing the OS rate. Also significant reductions of the occurrence rates and severity of acute skin reaction, neck fibrosis, trismus and xerostomia were noticed in the IMRT arm. However, there were no differences in the incidence of mucositis, hematological toxicity, hearing loss and radiation induced cranial neuropathy between both modalities [20].

Moretto and colleagues in their study on 52 patients with stage I–IVB cancer nasopharynx treated with IMRT (26 patients) and 2D Rth / 3D conformal radiotherapy (26 patients) with chemotherapy in the majority of patients reported a 5-yr OS rate at 79 %, 5-yr local control rate at 78 % and, a 5-yr disease free survival at 65 % with no statistically significant differences between IMRT and 2DRT/3DCRT [21].

In this retrospective study, we aim to compare between IMRT and conventional 2D Rth as regards treatment outcome as a primary objective and treatment related morbidities as secondary objective in patients with non metastatic squamous cell carcinoma of the nasopharynx.

Patients and Methods:

Patients Cohort

The files of patients with biopsy proven nasopharyngeal squamous cell carcinoma who had been treated by radiotherapy with or without chemotherapy between January 2013 and January 2023 in the Department of Clinical Oncology, Sohag University Hospital were retrospectively analyzed. Patients from both sexes between 18 and 80 yrs who had been treated by IMRT or 2D Rth with or without chemotherapy have

been included. Radiological and pathological revision of the files should confirm the histopathology of squamous cell carcinoma and the stage being non metastatic. The patients should have no other cancers, no previous history of radiotherapy or chemotherapy. The minimum follow up period should be at least 3 month. No experimental drugs or experimental treatment modality were given to the patients. Patients consent on chemotherapy and radiotherapy should be present in their files. Patients with metastatic disease at presentation, recurrent disease and patients treated with palliative intent were not included in the study. The tumors were staged according to The International Union Against Cancer (UICC) / American Joint Committee on Cancer (AJCC) 2010 staging system based on clinical examination, endoscopy and CT/MRI scan of the head and neck, chest, abdomen and pelvis. Dental examination before beginning treatment was usually carried out. Treatment related toxicities scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.

Treatment methods

All patients received radiotherapy either by 2D Rth or IMRT with or without chemotherapy were enrolled. All patients treated with IMRT underwent CT simulation while conventional 2D simulator was used in 2D Rth treatment planning. Proper immobilization was done for all patients prior to treatment by means of customized thermoplastic mask covering the head, neck and shoulders. In 2D Rth technique, 3 phases were used in all patients. Phase I consists of 2 lateral opposed facio cervical fields encompassing the primary tumor and enlarged neck nodes with a 3rd lower anterior neck field for the lower cervical and supraclavicular nodes. In this phase, the margins of the lateral opposed fields were modified according to the individual tumor extensions but usually had to be at least 2 cm beyond tumor extensions seen in the CT scan and should cover the base of skull and sphenoid sinus superiorly, 1- 2 cm behind the mastoid process posteriorly. Anteriorly, including the posterior third of the maxillary sinus and nasal cavity with the posterior ethmoid air cells. Inferiorly the lateral field's margin was matching with the upper margin of the anterior neck field. This later field was usually extending from the lower border of the sternoclavicular joint inferiorly to the matching line with the lateral opposed fields superiorly and laterally at 1 cm lateral to the intersection of the first rib with the clavicle. The apex of each lung and the larynx were protected with appropriate blocks. A midline dose at 40 Gy was routinely given.

In phase II, the posterior border of the facio cervical fields is displaced anteriorly after 40 Gy to keep the spinal cord and dose escalation of 10 Gy was given to the shrunken fields. The posterior neck nodes were given a supplementary dose of 10 Gy with 9-Mev electrons through small lateral fields. The dose to the lower neck field was at 50 Gy prescribed at 3 cm depth. After 50 Gy , in phase III, the lateral opposed fields were reduced to include a margin of 1.5 to 2 cm around the primary tumor and any enlarged nodes with dose escalation up to 66 – 70 Gy. All doses were given in 2 Gy per session, 5 sessions per week.

In case of IMRT, the patients underwent CT simulation after proper immobilization. CT simulation was performed at 3 – 5 mm intervals. CT images were imported onto treatment planning system. GTV included all known gross disease as evaluated by clinical examination, endoscopy, contrast-enhanced CT and/or MRI. When neoadjuvant chemotherapy was used, the pre treatment tumor volume was taken into consideration.

Clinical target volume (CTV), planning target volume (PTV), organs at risk (OAR) and planning organ at risk volume (PRV) were defined according to the International Commission on Radiation Units and Measurements (ICRU) report 83 recommendations [22]. Brain stem, optic nerves, optic chiasm, spinal cord, temporal lobes, larynx, cochlea/vestibule, oral cavity and parotid glands were contoured as organs at risk during optimization. The dose constraints set at < 54 Gy for brain stem, optic nerve and chiasm, < 45 Gy for spinal cord, < 63 Gy for temporal lobe, < 50 Gy for larynx, < 50 Gy for cochlea/vestibule, < 41.8 Gy for oral cavity and, for the parotid gland, the mean dose < 25 Gy. A 5-mm margin was added to the spinal cord and brain stem to form the planning organ at risk volume (PRV).

High risk primary clinical target volume (CTV-primary) that received 66 – 70 Gy was defined as 5 mm margin around GTV primary. Similarly, high risk nodal CTV (received 66 - 70 Gy) included corresponding GTV plus 5 mm margin and 10 mm in case of extra nodal extension.

The intermediate risk CTV tumor (received 60 Gy) included the CTV primary plus 5 mm and those areas with high risk of hosting microscopic disease. It included the entire nasopharynx, entire clivus if clinically involved or the anterior 1/2 to 2/3 of the clivus, inferior sphenoid sinus, skull base including foramen ovale and rotundum, pterygoid fossa, parapharyngeal space, and posterior one-third of nasal cavity and maxillary sinuses. The intermediate risk CTV nodal (received 60 Gy) included bilateral levels II, III, and V, retrostyloid, and retropharyngeal lymph nodes to the level of hyoid bone. If level III nodes were involved clinically, then level IV and supraclavicular lymph nodes were also included in CTV nodal receiving 60 Gy. Level Ia was included if submandibular nodes or oral cavity was involved by cancer and level Ib (submandibular nodes) was electively irradiated only if there was nodal disease on the ipsilateral neck.

The low-risk CTV (received 54 Gy) included the bilateral uninvolved lower cervical nodal groups. A 5 mm volumetric expansion was used to generate the planning target volumes (PTV) from the corresponding CTVs. Dose constraints for organs at risk (OAR) were often prescribed according to Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report [23].

IMRT plans were generated using an inverse planning algorithm. Plans were optimized to deliver

100% of the prescribed dose to at least 95% of the PTV, up to 10% of PTV to receive ≥ 107% of the prescribed dose and the maximum dose to critical organs kept within the tolerance limits

Patients were treated in once daily fractions, 5 days a week for a total duration of 6-7 weeks. Planning was done with Varian Eclipse treatment planning system and treatment was delivered on Varian Unique linear accelerator 6 MV using step and shoot technique, sliding window technique or the Rapid Arc IMRT technique. A weekly portal imaging was taken to check for any set up errors.

To verify the treatment position, two orthogonal images of the treatment region were taken each 5 sessions by Electronic portal imaging Device (EPID) and matched with the digitally reconstructed radiographs (DRR) generated from the planning system.

Chemotherapy either concurrent or induction was administered to patients with stage ≥ II using cisplatin based regimen. CCRT was offered to patients with stage II and above disease using cisplatin at a dose of 80–100 mg/m2 on D1 every three weeks. Induction chemotherapy was given to patients with initial advanced disease usually with PF regimen (cisplatin at a dose of 75–100 mg/m2 IV infusion on day 1 and 5-fluorouracil 750–1000 mg/m2 IV continuous infusion on days 1–4, every three weeks).

All patients were reviewed weekly during radiotherapy. After completion of planned course of treatment, the patients were followed up at regular intervals with complete examination, basic serum chemistry, chest X-ray, ultrasound of abdomen and, flexible fiberoptic endoscopy. Re assessment CT scan of the head and neck was scheduled at four to six months posttreatment and thereafter as required. MRI of the head and neck areas was performed every 6 months.

Statistical analysis

The Chi square Test was used (as indicated) for comparisons of patients' basic characteristics and outcomes. A t-test is used to compare two sample means from unrelated groups. Survival curves were calculated by the Kaplan-Meier method. Differences between curves were analyzed by the log-rank test. OS was defined as the time between the date of diagnosis and last follow up or death from any cause. LPFS and DPFS were defined as the time between the date of diagnosis and last follow up or the first local or distant failure, respectively. All tests were two sided. A P value of < 0.05 was considered to be significant. Statistical analyses were performed using the SPSS software program (IBM SPSS Statistics version 13).

Ethical Approval

The study has IRB registration number: Soh-Med-23-10-01PD issued by The Medical Research Ethics Committee Faculty of Medicine-Sohag University.

Results:

Patient, disease characteristics and treatment delivery

A cohort of 41 patients is identified. Twenty one patients (51%) treated with IMRT and 20 patients (49%) treated with 2D Rth.

Ages of the patients in the whole cohort have ranged from 21 to 80 yr with a median at 51.5 y. Males (33 patients) represented the majority of patients (80%) while females (8 patients) represented (20%) of the whole cohort.

On presentation, lymphadenopathy, ear ache, nasal obstruction, epistaxis, headache and nasal discharge were reported in 30 (73%), 10 (24%), 4 (10%), 3 (7%), 2 (5%) and 1 (2%) patients respectively. History of smoking was reported in 7 patients (17%). All patients had no distant metastasis on presentation. Stage 2 presented in 20 (49%) of cases while stage 3 and 4 in 9 (22%) and 12 cases (29%) respectively. Radiotherapy in all patients was given in conventional fractionation at doses either 180 or 200 cGy/session. Doses at 70 Gy were reported in 20 patients (49%), while doses from 70 Gy down to 60 Gy were reported in 21 patients (51%) of the whole cohort.

History of chemotherapy was reported in 33 cases (80%). CCRT in 23 (56%), induction chemotherapy alone in 5 patients (12%) and both induction and CCRT in another 5 patients (12%). The follow up period in the whole cohort ranged from 3 to 120 month with a mean at 42 months.

As seen in table 1, both treatment groups (the 2D Rth and IMRT) were comparable in baseline characteristics apart from a significant association between the treatment technique and the stage of the tumor. While more patients with advanced stage have been treated with 2D Rth compared with the IMRT technique (14 vs 7 patients), patients with earlier stage have been more frequently treated with IMRT (14 vs 6 patient treated with 2D Rth; p=0.028). Another significant finding noticed in table 1 that is, the significant association between using higher doses of radiotherapy with IMRT (70 Gy vs < 70 Gy) compared to 2D Rth (14 vs 6 patients; p = 0.007).

Clinical outcomes

During treatment, radiotherapy associated acute side effects grade 3 – 4 included skin erythema, mucositis and dysphagia and were reported in 7/20 patients (35%) and 8/21 patients (38%) patients treated with 2D Rth and IMRT respectively (p=0. 0.597).

In the IMRT arm, 8/21 patients (38%) have developed mix of grade 3-4 late toxicities vs 11/20 patients (55%) in the arm treated with 2D Rth (p = 0.432) and included trismus, dental necrosis, xerostomia, mandibulitis and, subcutaneous fibrosis reported in 6 (28%), 4 (19%), 3 (14%), 2 (9%) and 2 (9%) patients respectively. In the 2D Rth arm tennitus, radionecrosis in skull base, maxillary sinusitis, nasal tone of speech and dysphagia were reported in 1 (5%), 1 (5%), 1 (5%), 1 (5%), 11 (55%) patients respectively. No severe abnormal laboratory findings were reported apart from cytopenia grade 4 in 3 patients (7%). Although these toxicities have occurred more frequently

with dose at 70 Gy than with lower doses and in advanced more than earlier stages, the association did not reach significant level either with these variables or with other variables such as age, technique of radiotherapy, history of chemotherapy, gender, performance status or history of smoking (all with p value > 0.05).

Overall, complete response (CR) was achieved in 22 patients (54%), partial response (PR) in 15 patients (36%), stable disease (SD) in 3 patients (7%) and progressive disease (PD) in 1 patient (2%) in the whole cohort. During follow up, death reported in 17 patients (41%) with a mean time at 42 m, local recurrence reported in 11 patients (27%) with a mean time at 34 m and, distant recurrence to lung, liver, bone and brain reported in 6 patients (15%) with a mean time at 41 m.

Survival analysis

The overall treatment effects in terms of overall survival (OS), local progression free survival (LPFS) and, distant progression free survival (DPFS) were analyzed in the whole cohort (table 2) and in the main subgroups of patients (table 3). As regards the 5-y OS, it was at 60% in the whole cohort (figure 1) with an estimated median OS at 110 m (95% CI: 18.03 – 201.96). It did not show significant difference between IMRT and 2D Rth (64% vs 72%; p = 0.218) as seen in table 2.

The 5-y LPFS (figure 2) was at 71% in the whole cohort with an estimated median LPFS at 110 m (95% CI: 98.72 – 121.27). Although it was higher with IMRT, the difference was not significant (85% vs 63% with 2D Rth; p = 0.220).

Concerning the 5-y DPFS (figure 3), it was at 80% in the whole cohort with an estimated median DPFS at 96 m (95% CI: 82.04 – 109.7 m). In spite of the better rate achieved with IMRT vs 2D Rth, the difference was not significant (88% vs 77%; p = 0.449).

As seen in table 2, the only variable that has significantly affected the OS in the whole cohort in univariate analysis was age of the patients. Those at ≤ 51 y have gained significantly higher 5-y OS rate (80% vs 40%) and longer median OS compared to those aged > 51 y (p = 0.049) as shown in figure 4. However, in multivariate analysis, younger age was associated with non significant decrease in hazard of death (HR: 0.392 & 95% CI: 0.125 – 1.232 & p = 0.085). As regards the other potential risk factors studied, although there have been some differences in the rates of OS between the subdivisions of these risk factors which included technique of irradiation, radiation dose, addition of chemotherapy in treatment, stage of the disease, gender of the patients and history of smoking, these differences did not significantly affect the OS in the whole cohort of patients as seen in table 2. Concerning the 5-y LPFS and 5-y DPFS, there was also non significant differences between the subdivisions of the studied potential risk factors mentioned above as shown in table 2.

In subgroup analysis (table 3), the main patients subgroups expected to have treatment effects different from the general cohort were analyzed. The subgroup of patients treated with 2D Rth and that treated with IMRT (20 and 21 patients respectively) showed no significant differences in the subdivisions of the studied variables as shown in table 3A and 3B respectively but, in the subgroup of patients with stage II (20 patients), IMRT was associated with significantly higher 5-y DPFS when compared with the conventional 2D Rth (p=0.049) in univariate analysis as shown in table 3C and figure 5. However, in multivariate analysis, the treatment technique did not significantly affect the 5-y DPFS (HR: 1.414 & 95% CI: 0.85 – 23.5 & p = 0.980) for 2D Rth versus IMRT.

In the subgroup with advanced stage III / IV, no significant differences were noticed between the subdivisions of the studied variables (table 3D).

In the subgroup of patients received chemotherapy in their treatment either concomitant, induction or both induction and concomitant (33 patients, table 3E), a significantly higher 5-y OS rate was observed in younger than older patients in univariate analysis (75% vs 26%; p = 0.047) as shown in figure 6. However, in multivariate analysis, younger age was associated with non significant decrease in hazard of death (HR: 0.339 & 95% CI: 0.110 – 1.042 & p = 0.075). Addition of chemotherapy to radiotherapy has also shown significantly higher 5-y LPFS rate with advanced versus earlier stage (93% in stage III / IV vs 48% in stage II , p = 0.012) as shown in figure 7. However, in multivariate analysis, no significant association found (HR = 1.230 & 95 % CI: 0.170 – 8.879 & p = 0.250) for early versus advanced stage

The significant association between age of the patients and OS observed in the subgroup received chemotherapy in their treatment was also evident in the subgroup received CCRT (23 patients) as seen in table 3F and figure 8 (80% versus 16% for younger versus older patients, p = 0.011) in univariate analysis and also in multivariate analysis where younger age was significantly associated with decrease in hazard of death compared with older age (HR:0.123; 95% CI : 0.021 – 0.712 & p = 0.019).

In the subgroup of patients received 70 Gy (20 patients, table 3G, figure 9), patients with advanced stage have demonstrated significantly higher 5-y OS compared with earlier stage (81% versus 40% ; p = 0.041) in univariate analysis but not in multivariate one (HR : 1.57; 95% CI : 0.226 – 11.02 & p = 0.445) for earlier versus advanced stage.

Another significant observation was also observed in this subgroup between advanced stage and local recurrence free survival where the 5-y LPFS was significantly higher in advanced versus in earlier stage (p = 0.012) in univariate analysis but not in multivariate analysis (HR: 1.72; 95% CI: 0.165 – 18.02 & p = 0.650) for earlier versus advanced stage.

The last significant observation in our study was noticed in the subgroup of patients older than 51 y (table 3H and figure 11) where a significantly higher 5-y OS was evident in females than in males patients (p=0.020) in univariate analysis. However, in multivariate analysis such an association was not significant (HR: 0.975; 95% CI: 0.040 – 22.05 & p = 0.934) for females versus males patients.

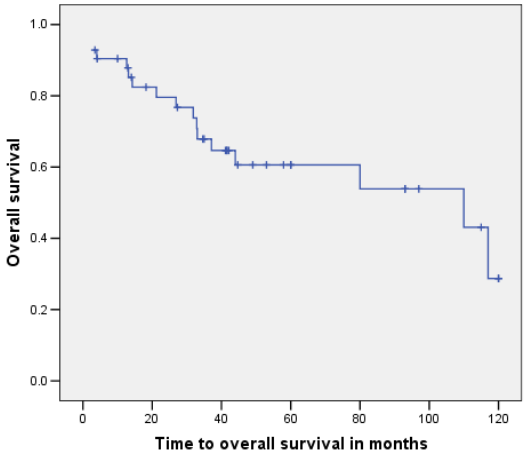

Figure 1. Overall survival in the whole cohort of patients.

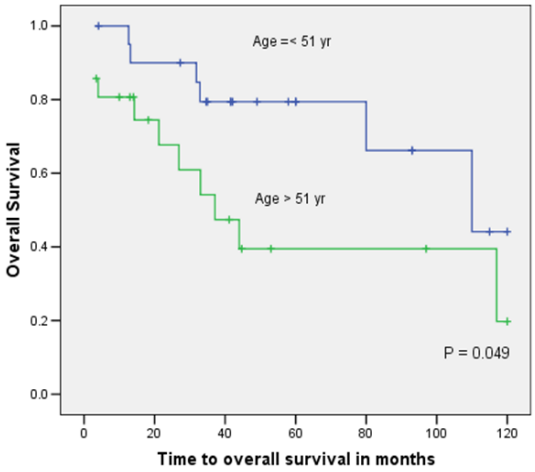

Figure 4. Significantly higher OS in younger than in older patients in the whole cohort of patients.

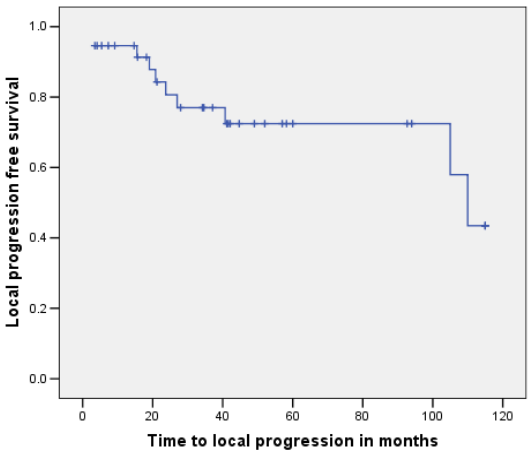

Figure 2. Local progression free survival in the whole cohort of patients.

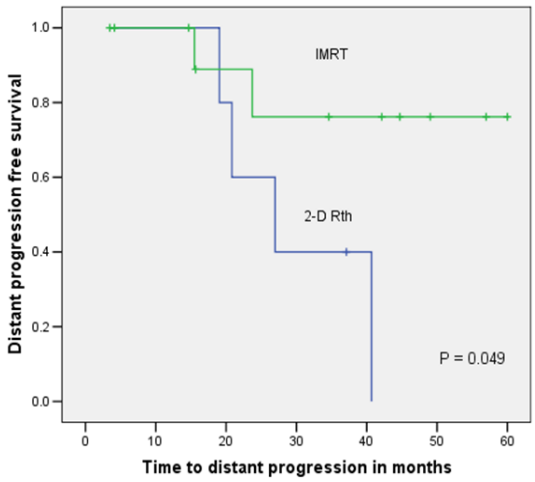

Figure 5. Significantly higher DPFS with IMRT vs 2D Rth in the subgroup with stage II.

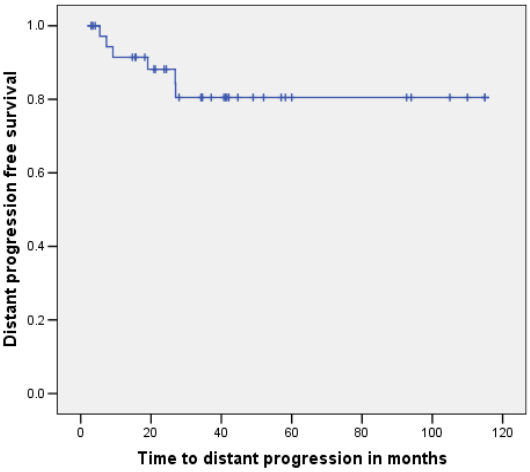

Figure 3. Distant progression free survival in the whole cohort of patients.

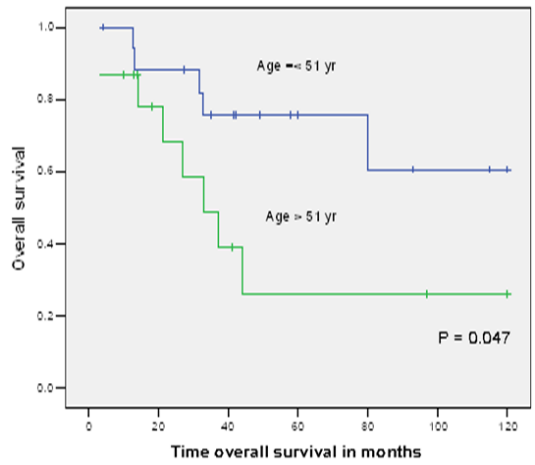

Figure 6. Significantly higher OS in younger than in older patients in the subgroup received chemotherapy in their treatment.

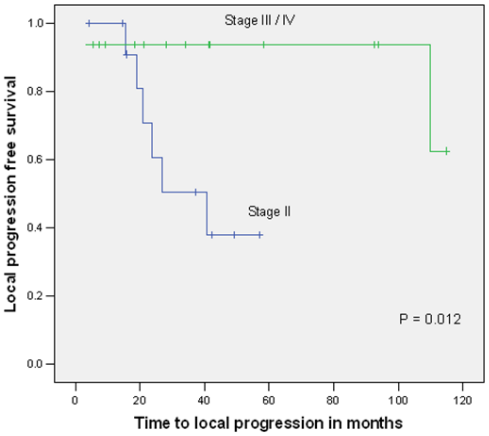

Figure 7. Significantly higher LPFS in advanced versus earlier stage of the tumor in the subgroup received chemotherapy in their treatment.

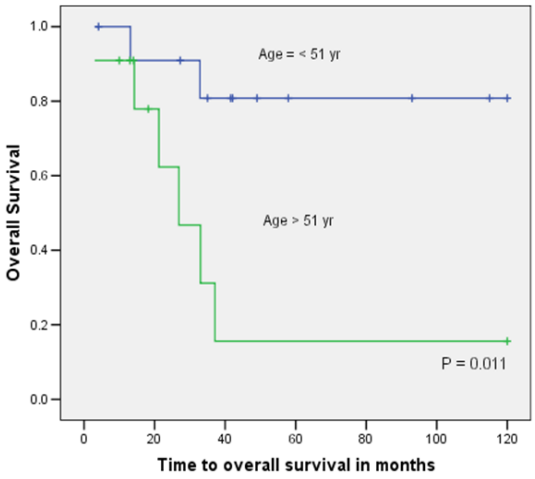

Figure 8. Significantly higher OS in younger versus older patients in the subgroup received CCRT.

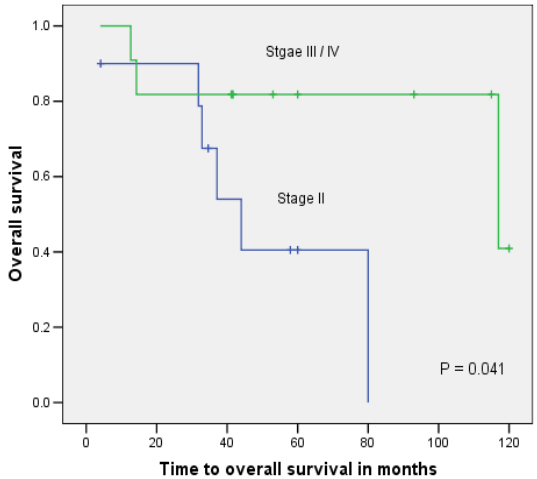

Figure 9. Significantly higher OS in advanced versus earlier stage in the subgroup irradiated at 70 Gy

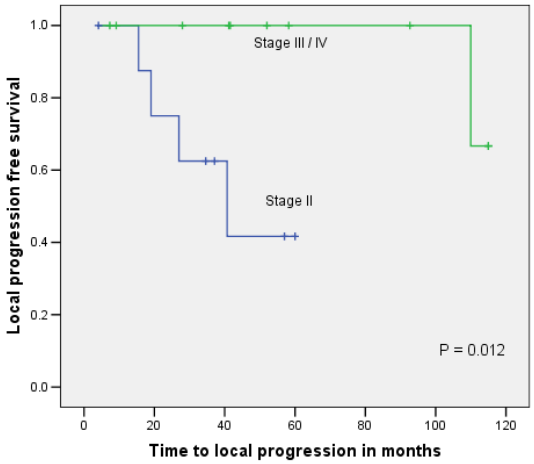

Figure 10. Significantly higher LPFS in advanced versus earlier stage in the subgroup irradiated at 70 Gy

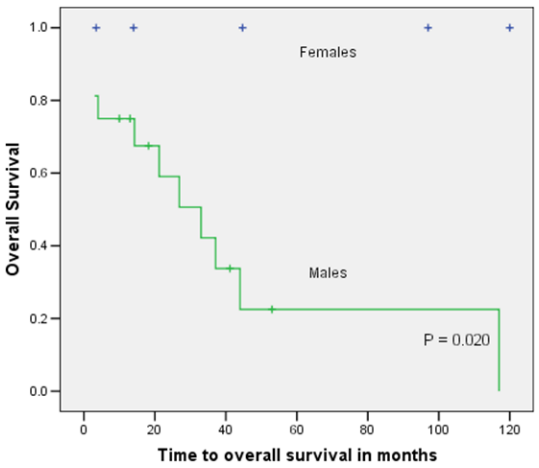

Figure 11. Significantly higher OS in females versus males in the subgroup aged > 51 yr.

Table 1. Clinicopathologic characteristics of the whole patients

Characteristic	***2D Rth (n = 20 pt)***	***IMRT (n = 21 pt)***	***Chi Square value***	***p***
Mean Age of the patients	54 y	49 y	Not applicable	0.379
Mean follow up in months	60 month	32 month	Not applicable	0.057
Sex				
Males	18 (44%)	15 (36%)	2.25	0.134
Females	2 (5%)	6 (15%)		
Performance status				
1	5 (12%)	12 (29%)	0.403	0.428
2	3 (7%)	4 (10%)		
History of smoking				
Smokers	4 (10%)	3 (7%)	2.23	0.266
Non smokers	1 (2%)	5 (12%)		
Stage of the disease				
Stage II	6 (15%)	14 (34%)	4.91	0.028
Stage III / IV	14 (34%)	7 (17%)		
History of all chemotherapy schedules (induction alone, concurrent, both schedules)				
Yes	16 (39%)	17 (41%)	0.087	0.534
No	4 (10%)	4 (10%)		
History of concurrent chemoradiotherapy (CCRT)				
Yes	11 (27%)	12 (29%)	0.019	0.570
No	9 (22%)	9 (22%)		
Dose of irradiation				
< 70 Gy	14 (34%)	7 (17%)	7.54	0.007
70 Gy	6 (15%)	14 (34%)		

Table 2. Survival outcomes in the whole cohort in univariate analysis

Variable	*Estimated median OS in month (95% CI)*	*5-y OS*	*p*	*Estimated median LPFS in months (95% CI)*	*5-y LPFS*	*p*	*Estimated median DPFS in months (95% CI)*	*5-y DPFS*	*p*
Rth technique									
2D Rth	80 (3.3 – 156 m)	72%	0.218	110 (26 – 194 m)	63%	0.220	Not estimated	77%	0.449
IMRT	Not estimated	64%		Not estimated	85%		Not estimated	88%	
Rth dose									
< 70 Gy	Not estimated	72%	0.791	Not estimated	72%	0.860	Not estimated	76%	0.936
70 Gy	110 (28 – 192 m)	73%		110 (100 –120 m)	75%		Not estimated	80%	
All Cth									
Yes	80 (18 – 201 m)	55%	0.990	110 (0.00 – 220 m)	68%	0.668	Not estimated	77%	0.200
No	110 (0.00 – 262 m)	76%		105 (0.00 – 248 m)	88%		Not estimated	Cens	
Concurrent Cth (CCRT)									
Yes	Not estimated	55%	0.868	110 (98 --- 121 m)	72%	0.925	Not estimated	80%	0.987
No	110 (65 – 155 m)	69%		105 (13 – 196m)	72%		Not estimated	80%	
Age									
≤ 51 y	110 (56 – 164 m)	80%	0.049	105 (46 –164m)	75%	0.935	Not estimated	85%	0.642
> 51 y	37 (17 – 57 m)	40%		Not estimated	70%		Not estimated	70%	
Sex									
Males	80 (9 – 150m)	56%	0.120	110 (39 –180m)	70%	0.370	Not estimated	76%	0.211
Females	Not estimated	82%		Not estimated	82%		Not estimated	Cens	
Smoking history									
Yes	Not estimated	83%	0.937	Not estimated	No	0.221	Not estimated	Cens	0.398
No	Not estimated	76%		Not estimated	plot		Not estimated	Cens	
Stage									
Stage II	80 (27 – 133m)	56%	0.972	Not estimated	55%	0.092	Not estimated	82%	0.525
Stage III / IV	117 (0.00 – 274m)	60%		Not estimated	80%		Not estimated	77%	

Table 3. Survival outcome in the main subgroups of the study in univariate analysis

Table 3A. Survival outcomes in the subgroup of patients treated with conventional 2 D Rth (20 patients)

Variable	*Estimated median OS in months (95% CI)*	*5-y OS*	*p*	*Estimated median LPFS in months (95% CI)*	*5-y LPFS*	*p*	*Estimated median DPFS in months (95% CI)*	*5-y DPFS*	*p*
Rth dose									
< 70 Gy	37 (22 – 51 m)	35%	0.246	Not estimated	65%	0.906	Not estimated	Cens	0.356
70 Gy	117 (0.00 – 290 m)	60%		110 (36 –183 m)	70%		Not estimated	70%	
All Cth									
Yes	80 (not estimated)	55%	0.234	110 (0.00 – 237m)	60%	0.739	Not estimated	70%	0.427
No	4 (0.00 – 108 m)	50%		105 (0.00 – 268m)	65%		Not estimated	Cens	
Concurrent Cth (CCRT)									
Yes	37 (not estimated)	50%	0.443	110 (not computed)	71%	0.610	Not estimated	87%	0.591
No	80 (0.00 – 179 m)	57%		105 (9 – 200 m)	605		Not estimated	70%	
Age									
≤ 51 y	110 (53 – 166 m)	78%	0.181	105 (0.00 – 233 m)	60%	0.537	Not estimated	77%	0.900
> 51 y	37 (7 – 66 m)	34%		Not estimated	67%		Not estimated	70%	
Sex									
Males	Not estimated	50%	0.121	Not estimated	57%	0.201	Not estimated	70%	0.427
Females	Not estimated	Cens		Not estimated	Cens		Not estimated	Cens	
Smoking history									
Yes	Not estimated	75%	0.617	Not estimated	Cens	No	Not estimated	Cens	0.617
No	Not estimated	Cens		Not estimated	Cens	plot	Not estimated	Cens	
Stage									
Stage II	39 (25 – 53 m)	39%	0.256	26 (13 – 40 m)	NR	0.075	Not estimated	Cens	0.436
Stage III / IV	112 (0.00 – 270 m)	59%		Not estimated	84%		Not estimated	80%	

Table 3B. Survival outcomes in the subgroup of patients treated with IMRT (21 patients)

Variable	*Estimated median OS in month (95% CI)*	*5-y OS*	*p*	*Estimated median LPFS in months(95% CI)*	*5-y LPFS*	*p*	*Estimated median DPFS in months(95% CI)*	*5-y DPFS*	*p*
Rth dose									
< 70 Gy	Not estimated	NR	0.294	Not estimated	No	0.949	Not estimated	NR	0.180
70 Gy	Not estimated	88%		Not estimated	plot		Not estimated	100%	
All Cth									
Yes	Not estimated	57%	0.114	Not estimated	NR	0.325	Not estimated	80%	0.357
No	Not estimated	Cens		Not estimated	Cens		Not estimated	Cens	
Concurrent Cth (CCRT)									
Yes	Not estimated	60%	0.183	Not estimated	NR	0.240	Not estimated	75%	0.274
No	Not estimated	Cens		Not estimated	Cens		Not estimated	Cens	

Age									
≤ 51 y	Not estimated	80%	0.354	Not estimated	No	0.572	Not estimated	No	0.608
> 51 y	33 (not estimated)	NR		Not estimated	plot		Not estimated	plot	
Sex									
Males	Not estimated	70%	0.839	Not estimated	No	0.486	Not estimated	80%	0.383
Females	Not estimated	Cens		Not estimated	plot		Not estimated	Cens	
Smoking history									
Yes	Not estimated	Cens	0.414	Not estimated	No	0.317	Not estimated	No	---
No	Not estimated	Cens		Not estimated	plot		Not estimated	plot	
Stage									
Stage II	Not estimated	75%	0.579	Not estimated	75%	0.288	Not estimated	Cens	0.097
Stage III / IV	Not estimated	70%		Not estimated	NR		Not estimated	68%	

Table 3C. Survival outcomes in the subgroup of patients with stage II (20 patients)

Variable	***Estimated median OS in month (95% CI)***	***5-y OS***	***p***	***Estimated median LPFS in months(95% CI)***	***5-y LPFS***	***p***	***Estimated median DPFS in months(95% CI)***	***5-y DPFS***	***p***
Rth technique									
2D Rth	37 (22 – 52m)	33%	0.144	27 (14 –40m)	NR	0.068	Not estimated	NR	0.049
IMRT	Not estimated	75%		Not estimated	77%		Not estimated	100%	
Rth dose									
< 70 Gy	Not estimated	80%	0.109	Not estimated	NR	0.658	Not estimated	Cens	0.244
70 Gy	44 (30 – 58m)	40%		40 (14 – 67m)	40%		Not estimated	70%	
All Cth									
Yes	44 (6 –82m)	50%	0.654	Not estimated	NR	0.121	Not estimated	NR	0.372
No	Not estimated	75%		Not estimated	Cens		Not estimated	Cens	
Concurrent Cth (CCRT)									
Yes	Not estimated	57%	0.550	Not estimated	NR	0.960	Not estimated	NR	0.163
No	80 (27 – 133 m)	55%		40 (14 – 67m)	45%		Not estimated	70%	
Age									
≤ 51 y	80 (13 –147m)	78%	0.091	Not estimated	50%	0.968	Not estimated	No	0.586
> 51 y	37 (28 – 45m)	NR		30 (not estimated)	NR		Not estimated	plot	
Sex									
Males	80 (34 – 126m)	50%	0.609	40 (7—74m)	40%	0.487	Not estimated	75%	0.372
Females	Not estimated	NR		Not estimated	NR		Not estimated	Cens	
Smoking history									
Yes	Not estimated	No	0.480	Not estimated	No	0.317	Not estimated	No	---
No	Not estimated	plot		Not estimated	plot		Not estimated	plot	

Table 3D. Survival outcomes in the subgroup of patients with stage III / IV (21 patients)

Variable	*Estimated median OS in month (95% CI)*	*5-y OS*	*p*	*Estimated median LPFS in months(95% CI)*	*5-y LPFS*	*p*	*Estimated median DPFS in months(95% CI)*	*5-y DPFS*	*p*
Rth technique									
2D Rth	117 (0.00 – 290m)	60%	0.627	Not estimated	85%	0.323	Not estimated	82%	0.607
IMRT	Not estimated	70%		Not estimated	NR		Not estimated	70%	
Rth dose									
< 70 Gy	27 (15 – 38m)	40%	0.360	Not estimated	No	0.564	Not estimated	55%	0.416
70 Gy	117 (0.00 – 262m)	80%		Not estimated	plot		Not estimated	83%	
All Cth									
Yes	Not estimated	60%	0.578	Not estimated	100%	0.512	Not estimated	74%	0.445
No	117 (not estimated)	67%		Not estimated	67%		Not estimated	Cens	
Concurrent Cth (CCRT)									
Yes	Not estimated	50%	0.684	Not estimated	90%	0.808	Not estimated	68%	0.339
No	117 (not estimated)	80%		Not estimated	90%		Not estimated	88%	
Age									
≤ 51 y	Not estimated	80%	0.157	110 (not estimated)	100%	0.598	Not estimated	80%	0.993
> 51 y	27 (0.00 ---111m)	50%		Not estimated	80%		Not estimated	77%	
Sex									
Males	Not estimated	57%	0.207	Not estimated	90%	0.446	Not estimated	75%	0.445
Females	Not estimated	Cens		Not estimated	Cens		Not estimated	Cens	
Smoking history									
Yes	Not estimated	80%	0.527	Not estimated		-----	Not estimated	No	0527
No	Not estimated	Cens		Not estimated	----		Not estimated	plot	

Table 3E. Survival outcomes in the subgroup of patients received chemotherapy (33 patients)

Variable	*Estimated median OS in month (95% CI)*	*5-y OS*	*p*	*Estimated median LPFS in months(95% CI)*	*5-y LPFS*	*p*	*Estimated median DPFS in months(95% CI)*	*5-y DPFS*	*p*
Rth technique									
2D Rth	80 (not estimated)	55%	0.716	110 (0.00 –237 m)	60%	0.534	Not estimated	70%	0.606
IMRT	Not estimated	65%		Not estimated	72%		Not estimated	80%	
Rth dose									
< 70 Gy	Not estimated	58%	0.938	Not estimated	68%	0.777	Not estimated	73%	0.749
70 Gy	80 (0.66 – 159 m)	60%		110 (10 – 209 m)	67%		Not estimated	72%	
Age									
≤ 51 y	Not estimated	75%	0.047	110 (11 – 210 m)	70%	0.865	Not estimated	81%	0.543
> 51 y	33 (17 – 48 m)	27%		Not estimated	60%		Not estimated	61%	
Sex									
Males	80 (16 – 143 m)	51%	0.312	110 (10 – 209 m)	65%	0.591	Not estimated	70%	0.263

Females	Not estimated	75%		Not estimated	75%		Not estimated	Cens	
Smoking history									
Yes	Not estimated	No	0.949	Not estimated	No	0.264	Not estimated	No	0.361
No	Not estimated	plot		Not estimated	plot		Not estimated	plot	
Stage									
Stage II	44 (5 – 82m)	47%	0.918	41 (17 – 64 m)	40%	0.012	Not estimated	76%	0.633
Stage III / IV	Not estimated	60%		Not estimated	94%		Not estimated	75%	

Table 3F. Survival outcomes in the subgroup received concurrent chemo radiotherapy (23 patients)

Variable	***Estimated median OS in month (95% CI)***	***5-y OS***	***p***	***Estimated median LPFS in months(95% CI)***	***5-y LPFS***	***p***	***Estimated median DPFS in months(95% CI)***	***5-y DPFS***	***p***
Rth technique									
2D Rth	37 (not estimated)	50%	0.619	110 (not estimated)	72%	0.761	Not estimated	86%	0.887
IMRT	Not estimated	59%		not estimated	73%		Not estimated	78%	
Rth dose									
< 70 Gy	Not estimated	60%	0.927	Not estimated	69%	0.986	Not estimated	74%	0.795
70 Gy	Not estimated	58%		110 (0.00 – 245 m)	83%		Not estimated	86%	
Age									
≤ 51 y	Not estimated	80%	0.011	110 (0.00 – 237 m)	79%	0.864	Not estimated	100%	0.356
> 51 y	27 (13 – 41 m)	16%		Not estimated	60%		Not estimated	60%	
Sex									
Males	Not estimated	51%	0.580	110 (0.00 – 233 m)	75%	0.913	Not estimated	77%	0.381
Females	Not estimated	67%		Not estimated	68%		Not estimated	Cens	
Smoking history									
Yes	Not estimated	No	0.414	Not estimated	No	---	Not estimated	No	---
No	Not estimated	plot		Not estimated	plot		Not estimated	plot	
Stage									
Stage II	Not estimated	58%	0.372	Not estimated	59%	0.333	Not estimated	Cens	0.097
Stage III / IV	Not estimated	52%		Not estimated	90%		Not estimated	67%	

Table 3G. Survival outcomes in the subgroup received a dose of irradiation at 70 Gy (20 patients)

Variable	***Estimated median OS in month (95% CI)***	***5-y OS***	***p***	***Estimated median LPFS in months(95% CI)***	***5-y LPFS***	***p***	***Estimated median DPFS in months(95% CI)***	***5-y DPFS***	***p***
Rth technique									
2D Rth	80 (0.00 – 169 m)	55%	0.215	110 (36 – 184 m)	70%	0.583	Not estimated	NR	0.132
IMRT	Not estimated	86%		Not estimated	85%		Not estimated	70%	
All Cth									
Yes	80 (0.66 – 159 m)	58%	0.826	110 (10 – 210 m)	68%	0.360	Not estimated	71%	0.212
No	110 (0.00 – 261 m)	83%		105 (not estimated)	100%		Not estimated	Cens	
Concurrent Cth (CCRT)									

Yes	Not estimated	58%	0.640	110 (0.00 – 245 m)	83%	0.704	Not estimated	88%	0.770
No	110 (49 – 171 m)	69%		105 (13 – 197 m)	72%		Not estimated	78%	
Age									
≤ 51 y	110 (64 – 156 m)	77%	0.660	105 (13 – 197 m)	73%	0.148	Not estimated	83%	0.524
> 51 y	44 (0.00 – 119 m)	48%		Not estimated	83%		Not estimated	70%	
Sex									
Males	110 (36 – 184 m)	67%	0.464	110 (54 – 166 m)	80%	0.934	Not estimated	77%	0.424
Females	Not estimated	68%		Not estimated	67%		Not estimated	Cens	
Smoking history									
Yes	117 (not estimated)	80%	0.560	Not estimated	No	0.157	Not estimated	No	---
No	32 (not estimated)	NR		Not estimated	plot		Not estimated	plot	
Stage									
Stage II	44 (30 – 58 m)	40%	0.041	41 (41 – 67 m)	41%	0.012	Not estimated	70%	0.764
Stage III / IV	117 (0.00 – 262 m)	81%		Not estimated	100%		Not estimated	81%	

Table 3H. Survival outcomes in the subgroup of patients aged > 51 years (21 patients)

Variable	***Estimated median OS in month (95% CI)***	***5-y OS***	***p***	***Estimated median LPFS in months(95% CI)***	***5-y LPFS***	***p***	***Estimated median DPFS in months(95% CI)***	***5-y DPFS***	***p***
Rth technique									
2D Rth	37 (7 – 66 m)	33%	0.317	Not estimated	66%	0.662	Not estimated	73%	0.951
IMRT	33 (not estimated)	50%		Not estimated	66%		Not estimated	NR	
Rth dose									
< 70 Gy	27 (15 – 38 m)	NR	0.526	23 (not estimated)	No	0.275	27 (not estimated)	NR	0.886
70 Gy	44 (0.00 – 118 m)	50%		Not estimated	plot		Not estimated	73%	
All Cth									
Yes	33 (17 – 48 m)	28%	0.689	Not estimated	60%	0.747	Not estimated	60%	0.247
No	117 (not estimated)	63%		Not estimated	80%		Not estimated	Cens	
Concurrent Cth (CCRT)									
Yes	27 (13 – 41 m)	18%	0.266	Not estimated	60%	0.702	Not estimated	60%	0.311
No	117 (not estimated)	60%		Not estimated	73%		Not estimated	85%	
Sex									
Males	28 (16 – 40 m)	22%	0.020	Not estimated	55%	0.159	Not estimated	60%	0.227
Females	Not estimated	Cens		Not estimated	Cens		Not estimated	Cens	
Smoking history									
Yes	Not estimated	No	---	Not estimated	No	---	Not estimated	No	---
No	Not estimated	plot		Not estimated	plot		Not estimated	plot	
Stage									
Stage II	37 (29 – 45 m)	NR	0.990	27 (not estimated)	NR	0.712	Not estimated	NR	0.897
Stage III / IV	27 (0.00 – 111 m)	48%		Not estimated	80%		Not estimated	73%	

Table 3I. Survival outcomes in the subgroup of patients aged ≤ 51 years (20 patients)

Variable	*Estimated median OS in month (95% CI)*	*5-y OS*	*p*	*Estimated median LPFS in months(95% CI)*	*5-y LPFS*	*p*	*Estimated median DPFS in months(95% CI)*	*5-y DPFS*	*p*
Rth technique									
2D Rth	110 (53 – 166 m)	77%	0.824	105 (0.00 – 233 m)	60%	0.267	Not estimated	77%	0.483
IMRT	Not estimated	81%		Not estimated	NR		Not estimated	90%	
Rth dose									
< 70 Gy	Not estimated	83%	0.389	Not estimated	80%	0.362	Not estimated	84%	0.982
70 Gy	110 (64 – 156 m)	78%		105 (13 – 197 m)	72%		Not estimated	83%	
All Cth									
Yes	Not estimated	75%	0.858	110 (11 – 209 m)	70%	0.931	Not estimated	80%	0.447
No	110 (not estimated)	100%		105 (not estimated)	100%		Not estimated	Cens	
Concurrent Cth (CCRT)									
Yes	Not estimated	80%	0.251	110 (0.00 – 237 m)	80%	0.483	Not estimated	91%	0.483
No	110 (not estimated)	78%		105 (not estimated)	70%		Not estimated	77%	
Sex									
Males	110 (not estimated)	83%	0.661	110 (53 – 166 m)	77%	0.481	Not estimated	82%	0.481
Females	Not estimated	NR		Not estimated	NR		Not estimated	Cens	
Smoking history									
Yes	Not estimated	No	1.000	Not estimated	No	0.317	Not estimated	No	0.317
No	Not estimated	plot		Not estimated	plot		Not estimated	plot	
Stage									
Stage II	80 (13 – 147 m)	78%	0.704	Not estimated	52%	0.059	Not estimated	90%	0.455
Stage III / IV	Not estimated	78%		110 (not estimated)	100%		Not estimated	77%	

Abbreviations: Cens : censored, NR : not reached.

Discussion:

In this retrospective study we report our experience with IMRT in treatment of patients with non metastatic nasopharyngeal carcinoma. After a follow up period ranged between 3 and 120 m, we have found the 5-yr OS, LPFS and DPFs rates were at 64%, 85% and 88% for IMRT. Such rates are more closer to these reported in a small study conducted by Moretto et al [21] where the 5-y OS; LPFS and DFS rates were at 79%, 78% and 65% respectively yet less closer to those reported in a much larger study like that conducted by OuYang et al where they found the 5-yr OS, loco-regional relapse free survival and distant metastasis-free survival (DMFS) rates at 91.3%, 92.3% and 92.9% respectively in IMRT treated patients [19].

A significant association between age and OS in the whole cohort was found in our study. As seen in table 2 and figure 4, the 5-y OS in patients ≤ 51 y is double that in older patients (80% vs 40%, p=0.049). Some researchers have reported that advanced age is a strong and independent predictor of poor disease-free survival and cancer-specific survival [24, 25], others have observed more mortality rates in patients > 60 y [26] and > 65 y [27]. There is no clear pathophysiological explanation for such a decreased treatment efficacy in older patients however, possible explanations could be poor tolerance, increased risk of toxicity leading to lower chemotherapy dose intensity [28]. Other explanations could include gradual decline in the functional status and the increase in the rate of comorbidities in elderly patients [29 – 31].

The second significant observation in our study relates to the modality of radiotherapy. Some studies reported that with IMRT, the local control, the 5-y disease specific survival (DSS) and the OS rates could reach 80% - 90%, 85% and 80% respectively in contrast to 2D Rth and conformal 3D Rth where DSS and OS rates have reached 80%, 71%, 81% and 73% respectively [32 – 35]. On the other hand, others have not found such an advantage [14, 19 - 21]. In our study, in spite of absence of an advantage of IMRT over 2D Rth in the whole cohort of patients on the level of OS, LPFS and DPFS, a significant improvement in 5-y DPFS was noticed in the subgroup with stage II disease in favor of IMRT compared with 2D Rth (p=0.049) as shown in table 3C and figure 5. A close finding was also reported in a larger study conducted by Lai SZ et al where they found equivalent results in both 2D Rth and IMRT on the level of local relapse-free survival (LRFS), nodal relapse-free survival (NRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS) however, in stage T1, IMRT has shown significant improvement of LRFS (p = 0.016) and a trend of improvement (without reaching statistical significance) in DFS compared with 2D Rth [33].

The third significant finding in our study was observed in the subgroup that included all schedules of chemotherapy in their course of treatment (33 patients). As seen in table 3E, patients ≤ 51 yr have shown significantly higher 5- y OS compared with those > 51 yr (p=0.047) in univariate analysis as seen in figure 6.

Another significant finding was also observed in this subgroup. As seen in figure 7 there is a significantly higher 5-y LPFS rate noticed in advanced versus earlier stage of the disease in univariate analysis (p= 0.012). This could be attributed to the effect of induction chemotherapy. Amongst the patients with stage II in this subgroup, 1 has received both induction and CCRT versus 4 with advanced stage (3% vs 12%, p = 0.049). Jiawang and colleagues reported that neoadjuvant (induction) chemotherapy before radical radiotherapy appeared to reduce distant metastasis and improve survival of non-metastatic N2-3 nasopharyngeal carcinoma patients [36].

The fifth significant finding in our study was noticed in the subgroup received CCRT. As seen in table 3F and figure 8, a significantly higher 5-y OS is noticed in younger than in older patients (80% versus 17% & p=0.011) in both univariate and multivariate analysis. Other investigators have reported that the benefit of chemotherapy decreased with increasing patient age > 60 yr [28].

The sixth significant notice in the current study was found in the subgroup irradiated to 70 Gy (table 3G) which included 20 patients, subdivided equally between stage II and stage III / IV. A significant association was observed between CCRT and stage. Nine patients in the advanced stage received CCRT versus 2 in the earlier stage (45% vs 10%; p = 0.048). That could explain why advanced stage in this subgroup has been associated with significantly higher 5-y OS and 5-y LPFS (figure 9 & 10 respectively) compared with earlier stage (81% versus 40%; p =0.041 and 100% versus 40%; p = 0.012 respectively). Some researchers have also observed improved outcome with higher radiation doses [37, 38]. Vikram et al. reported that patients received doses from 67 to 77 Gy had a higher rate of local control compared with those received doses from 57 to 67 Gy (P = 0.08) and a high rate of local control is possible even with advanced disease, if a sufficiently high dose of radiation is delivered [39].

The last significant observation in our study was regarding the influence of patient's gender on treatment outcome. As shown in table 3H and figure 11, patients in the older subgroup have shown significantly higher OS in females versus males (p=0.020). It is reported that the incidence of nasopharyngeal carcinoma is approximately 2.75 times higher in men than in women [40] that could be attributed to smoking, drinking and occupational risk factors [41].

The literature that reported on the influence of race and gender on mortality and outcome from nasopharyngeal carcinoma is sparse [42]. Guangli and colleagues in a study on 299 patients with non-disseminated nasopharyngeal carcinoma treated with IMRT demonstrated that for patients older than 45 yr, the 5-y OS was at 72.2% in males compared to 96.0% in females, p = 0.001[24]. Another study conducted by P-Y Ou Yang and colleagues, on 5929 patients, sex was found significant predictor of survival, with a definite advantage in females regardless of tumor stage [43]. Another study on 1,462 patients conducted by Linchong et al has found that women have a lower incidence and

mortality rate than men [44]. A finding that could be related to the inherent differences between sexes, especially in the level of sex hormones [24, 43, 45, 46].

As regards treatment related morbidities, studies concerning the late complications of 2D RT and IMRT from different radiotherapeutic centers varied greatly [47] and some published studies have either involved a small size, have short- to medium-term follow-up or did not include detailed analyses of late complications. The accurate correlation of dose with late toxicities from patients with dose–volume histogram (DVH) data and long follow-up is grossly lacking [48].

Many studies have shown that IMRT reduces overall adverse effects such as xerostomia and dysphagia, and thus improves quality of life, even when chemotherapy is added to IMRT [49], however, a prospective randomized study conducted by Michael and colleagues reported no significant difference in patient-reported severe xerostomia between IMRT and 2D Rth [50].

In our study, the radiotherapy technique did not significantly affect the incidence of late side effects in contrary to most published studies that could be attributed to the few number of patients enrolled. In the arm treated with IMRT, trismus was the most common side effect encountered as we did not use to contour mastication structures (masticator and pterygoid muscles) as organs at risk in our earlier days with IMRT due to their proximity to target volumes in advanced cases

Conclusion:

In this study we acknowledge that its retrospective design and the few number of patients have limited its power, however, we can recommend that IMRT should be applied whenever accessible to all patients with cancer nasopharynx especially in the early stage. Chemotherapy especially concurrent chemo radiotherapy and possibly induction + concurrent should be routinely applied whenever feasible especially in advanced stage. We also report that radiation dose ≥ 70 Gy is essential for disease control. Finally, both age and sex of the patient should be considered in risk factors that need to be focused on in larger prospective studies.

Conflict of interest

None

Authors′ contributions

First Author: Study design, writing and revision of the study

Second author: data collection, writing and revision of the study

Third author: writing, revision, tables and figures editing.

Fourth author: Study design, writing and revision

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