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Evaluation of Adaptive Radiation Therapy in Treatment of Locally Advanced Head and Neck cancers

Mostafa Mostafa
Assistant Lecturer of Clinical Oncology Faculty of Medicine Al-Azhar University, edr.darsh@gmail.com

Wael Elshishtawy
Associate Professor of Clinical Oncology Al-Azhar Faculty of medicin, waelheshish@gmail.com

Ahmed Al-Agamawi
Therapeutic Radiology and Nuclear Medicine, Al-Azhar University, ahmedagamawi@yahoo.com

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Evaluation of Adaptive Radiation Therapy in Treatment of Locally Advanced Head and Neck cancers

Mostafa El-Shahat Mostafa [1,*] Msc, Wael Helmy El-sheshtawy [1] MD, Ahmed Yousry ELAgamawy [1] MD

**Corresponding Author:*
Mostafa El-Shahat Mostafa
Edr.darsh@gmail.com

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[1]*clinical oncology and nuclear medicine Department, Luxor General Hospital, Egypt.*

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ABSTRACT

Background: Radiation therapy is the mainstay of treatment for locally advanced squamous cell carcinoma of the head and neck. During the course of treatment, intensity-modulated radiation therapy does not compensate for anatomical adjustments or tumor shrinkage. Adaptive radiotherapy may be a proposed solu¬tion to account these changes.
Aim of the work: to see how adaptive radiotherapy affects dosimetry and clinical effects in advanced squamous cell carcinoma of the head and neck.
Patients and methods: With a provisional diagnosis of locally advanced squamous cell carcinoma of the neck and head, 49 patients were treated with definitive concurrent chemoradiotherpay, with the initial plan improved to deliver 70 Gy. All patients have been resimulated at a median dosage of 42 Gy (range, 37.0-44.1) and shifted to adaptive plan.
Results: The median gross target volume and planning target volume increased by 0.74% and 1.66%, respectively, as a result of adaptive replaning. The ipsilateral, contralateral parotid, spinal cord, and brainstem maximum doses had a median reduction of 3.86%, 5.32%, 3.5% and 5.28, respectively. Median reduction in size of ipsilateral and contralateral parotid was 13.62% and 17.68% respectively. With a median 18-month follow-up period varying from (6.5 to 31), The median progression-free survival was not reached, but the cumulative PFS was 89.7% and 70.2% at one year and two years, respectively. The total survival rate at 1 year was 9.8%; at 2 years it was 83%.
Conclusion: Adaptive radiotherapy is a promising modality that offers the benefits of decreased radiation dosage to organs at risk and improvement in tumor coverage.

Keywords: *IMRT; Adaptive radiation; Advanced head and neck squamous cell carcinoma.*

INTRODUCTION

Radiotherapy is the cornerstone of the therapy for locally advanced head and neck cancer (AHNC), because of its ability to preserve organs instead of surgical resection with function loss, in addition to that radiotherapy increase the tumor control rate with acceptable toxicity profile in comparison to the surgery that may cause long term sever morbidity. [1]

Because of the high number of organs at risk in the small neck and head area, as well as the complexities of lymphatic drainage, as well as the high sensitivity of organs at risk to radiotherapy, which results in a high incidence of acute toxicity, intensity-modulated radiation therapy (IMRT) has become the primary strategy for such patients due to its ability to decrease dosages to organs at risk and cover different irregular targets with different dose gradients. [2]

During the radiotherapy course that likely extend to 6-7 weeks the tumor as well as some organs at risk like parotid glands change in size and location, these changes not taken in account during the traditional radiotherapy course although this may lead to a lack of target coverage and/or higher dosage for the organs at risk, because of this problem the idea of adaptive radiotherapy (ART) come to practice [3]

Many trials have tracked adjustments in target and risk organs throughout radiotherapy treatment courses throughout different schedules of CT, ranging between daily to weekly imaging and found significant geometrical changes that mandate adoptive replanting during the radiotherapy course for at least one time. References required [4]

If no adaptive replanning done routinely likely the coverage of the targeted will not be adequate along the treatment course, in addition to that organs at risk may receive radiation dose higher than what is seen in the primary plan and even exceed the predefined tolerance.[5]

The primary aim of this research is to assess the strategy of adaptive radiotherapy in advanced squamous cell carcinoma of the head and neck as regards dose to organ at risk (OAR) and dose to gross target volume (GTV), while the secondary aim is to assess the impact of tumor volume reduction rate (TVRR) on progression-free survival (PFS).

PATIENTS AND METHODS

Eligibility Criteria:

Age ≥ 18 years and ≤ 70 of both genders, Performance Status ≤ 2 ECOG scale, Histologically confirmed invasive Squamous cell carcinoma of the head and neck, Locally advanced tumors stage III and IVA (AJCC cancer staging system the 7th edition), Adequate laboratory investigations, Patients without any primary treatment for their current disease (surgical, chemotherapy, or radiotherapy); Informed consent.

Exclusion criteria:

Cellular subtypes other than squamous cell carcinoma, Pregnant women, Obese patients (> 120 kg); Sever skeletal deformity or any disease interfering with patient alignment and positioning of radiation therapy delivery.

Clinical examinations, ENT and dental evaluations, contrasted CT scans of the chest as well as upper abdomen, head and neck contrasted CT+MRI, and a series of laboratory investigations were performed on all patients to assess the degree of illness and the existence of comorbidity, if present.

Trial design:

Patients in this prospective study were given definitive IMRT (70 Gy/33 fractions) as well as weekly cisplatin 40 mg/m2 chemotherapy for seven weeks (weekly carboplatin AUC 2 allowed if impaired renal profile).

An IMRT treatment plan that covers 98% of the PTV with 95% of the treatment dosage while delivering 105% of the treatment dose to below 10%, and not delivering ≥ 110 of the treatment dose to the PTV.

Plans were generated concerning delivery using only 6-MV photons via linear accelerator (Varian Medical System). Quality assurance (QA) was done before starting treatment for every case; verification with an electronic portal image device (EPID) was done with the first three fractions, then weekly.

Adaptive design:

All patients at our study underwent to CT imaging for adaptive planning and radiological evaluation (off board) at the end of the 4th week (median dose 38.2 Gy). Adaptive replanning and new plan formation was done for all patients with comparing the clinical and dosimetric outcomes with original plan.

On the original CT scan, Plan 1 (P1) was defined as the original primary and boost plans (Original plan).

On rescan CT, Plan 2 (P2) was defined as the original primary and boost plans (new CT), with the calculation done without optimization to give us an accurate guide for dosimetric evaluation as regards the expected plan if the patient completed radiotherapy without adaptation.

On rescan CT, Plan 3 (P3) was defined as the original primary and adaptive boost (Adaptive plan).

Tumour Volume Reduction Rate (TVRR): has been calculated as ([pre-RT GTVt-rescan GTVt]/pre-RT GTVt), and the volume has been utilized to associate with survival differences (OS and PFS).

Follow up:

After finishing radiation course, radiological assessment was done after 6-8weeks with contrasted CT + MRI head and neck, endoscopy was done if required with/without biopsy upon need. Clinical and radiological evaluations were assessed based on Response assessment criteria (RECIST 1.1). Patients with PR, SD, and PD will be considered as locoregional failure. Patients with locoregional failure were evaluated for possible surgery for possibility for maximum locoregional control. If not candidate for surgery they received salvage chemotherapy.

Statistical methodology

The Statistical Package for Social Sciences (SPSS) versus 24 was used for data processing and analysis, with the mean, standard deviation, median, and range, Chi square, student t-test, linear correlation coefficient, and analysis of variance [ANOVA] tests. Survival analysis has been carried out utilizing the Kaplan-Meier method, and the P-value has been regarded as significant if it was less than 0.05.

Ethical Approval

Before the study began, the ethical committee of the faculty of medicine at Al-Azhar University granted approval.

RESULTS

The current prospective study involved 49 patients who fulfilled the eligibility criteria and had a pathologically confirmed locally advanced head and neck squamous cell carcinoma. Table (1) demonstrates the clinicopathological features of the patients.

The whole study group received IMRT radiation therapy with concurrent weekly cisplatin 40mg/m2, target volume coverage of original and boost plan on primary CT (P1), also doses to organs at risk (ipsilateral parotid, contralateral parotid, spinal cord as well as brain stem) are displayed in table (2)

The modified IMRT plan increased GTV and PTV2 median coverage by 0.25% and 0.1.27%, respectively; ipsilateral and contralateral parotid volumes were reduced by 13.26% and 17.68%, respectively. Table (3)

The median dose decrease to the ipsilateral parotid, contralateral parotid, spinal cord, and brain stem was 3.86%, 5.32%, 3.5%, and 5.28%, respectively, with adaptive replaning. The median coverage for GTV and PTV2 was improved by 0.25% and 0.1.27%, respectively, with the adapted IMRT plan. (Table 3)

Acute toxicities related to radiation therapy were assessed for all patients, grade III oral mucositis was developed in 36.7% of patients (5/49), grade III Xerostomia in 16.3% (8/49), grade III skin toxicity in 6.12% (3/49) and 34.6% of patients (17/49) developed grade III dysphagia (Table 4).

Response assessment was done after 8 weeks of finishing CCRTH. It was noticed that 65.3% of patients (32/49) had complete remission (CR), 24.48% (12/49) had partial response, 10.22% (5/49) had stationary disease (Table 5).

The mean pre-RT GTVt was 67.44 cm3 versus 45.78 cm3 for the adaptive GTVt. The calculated median Tumor volume reduction rate (TVRR) and relation with clinical outcomes are shown in table (6).

Based on the median change in TVRR, we looked at the impact of TVRR on DFS and OS, dividing patients into2 groups: TVRR <= 31.2 vs > 31.2 and results showed none statistically significant P-value (Table 7).

Variable		Total (49)	Percent (%)
Age (years)	Median:56.00		
	Range:(19-74)		
Gender	Male	35	71.4
	Female	14	28.6
Family history	Positive	1	2.04
	Negative	48	97.96
Smoking	Smokers	32	65.3
	Non-Smokers	17	34.7
Comorbidity	DM	14	28.6
	HTN	9	18.4
	(IHD)	3	6.1
	(HCV) Positive	3	6.1
PS (Performance Status)	0-1	48	97.96
	II	1	2.04
Clinical presentation	Hoarseness of voice	22	44.9
	Nasal obstruction	10	20.4
	Neck swelling	9	18.4
	Dysphagia	5	10.2
	Otalgia	3	6.1
Tumor site	Larynx	26	53.1
	Nasopharynx	15	30.6
	Oropharynx	6	12.3
	Hypopharynx	1	2.04
	External auditory canal	1	2.04
Grade	I	4	8.2
	II	21	42.8
	III	24	49.00
T stage	T2	6	12.3
	T3	18	36.7
	T4	25	51.0
N stage	N0	17	34.7
	N1	20	40.8
	N2	5	10.2
	N3	7	14.3
Stage	III	20	40.8
	IVA	29	59.2

Table 1: The clinicopathological characteristics of the study group.

		Plan 1 (original Plan on original CT)
		No. = 49
GTV volume (cm^3)	Median (IQR)	48.3 (26.8 – 74.1)
	Range	4.7 – 232.2
	Mean	67.442
	SD	64.7738
GTV 100%	Median (IQR)	98.94 (98.45 – 99.36)
	Range	98.14 – 99.95
PTV volume (cm^3)	Median (IQR)	126.2 (75.8 – 224.5)
	Range	19.4 – 855.9
PTV2 V95 (%)	Median (IQR)	95.84 (95.26 – 96.53)

Ipsilateral Parotid Volume (cm^3)	Range	94.16 – 97.58
	Median (IQR)	30 (23.5 – 37.3)
Ipsilateral Parotid Mean (Gy)	Range	17.7 – 49
	Median (IQR)	24.2 (22.6 – 24.6)
Contralateral Parotid volume (cm^3)	Range	16 – 25.8
	Median (IQR)	30.9 (25.8 – 37.3)
Contralateral Parotid Mean (Gy)	Range	19.5 – 48.1
	Median (IQR)	24.8 (23.1 – 25.2)
Spinal Cord Max (Gy)	Range	16.6 – 25.63
	Median (IQR)	42.6 (38.02 – 44)
Brain Stem Max (Gy)	Range	28.1 – 49.7
	Median (IQR)	41.4 (35.18 – 45.8)
	Range	6.4 – 54.13

Table 2: Target volumes and organs at risk of P1 (original Plan).

		Percentage change
		No. = 49
GTV volume (CC)	Median (IQR)	**-31.26 (-45.52 – -26.15)**
	Range	**-80.75 – 0**
GTV 100%	Median (IQR)	**0.25 (0 – 1.01)**
	Range	**(-0.05 – 2.08)**
PTV volume (CC)	Median (IQR)	**-22.81 (-36.21 – -8.11)**
	Range	**(-91.75 – -38.66)**
PTV 2 V95 (%)	Median (IQR)	**1.27 (0.57 – 2.09)**
	Range	**(-0.05 – 5.1)**
Ipsilateral Parotid Volume (cc)	Median (IQR)	**-13.62 (-21.72 – -9.81)**
	Range	**(-35.11 – -3.75)**
Ipsilateral Parotid Mean (Gy)	Median (IQR)	**-3.86 (-7.67 – 0)**
	Range	**(-32.41 – -4.46)**
Contralateral Parotid volume (cc)	Median (IQR)	**-17.68 (-22.41 – -8.41)**
	Range	**-47.15 – -12.26**
Contralateral Parotid Mean (Gy)	Median (IQR)	**-5.32 (-14.59 – -1.56)**
	Range	**(-33.59 – -0.35)**
Spinal Cord Max (Gy)	Median (IQR)	**-3.5 (-6.56 – 0)**
	Range	**(-33.25 – -1.89)**
Brain Stem Max (Gy)	Median (IQR)	**-5.28 (-7.92 – -2.13)**
	Range	**(-32.62 – -3.08)**

Table 3: Percentage of dose reduction for organ at risks after adaptation.

Toxicity	GI	GII	GIII	GIV	GV
Mucositis	5(10.2%)	16(32.6%)	18(36.7%)	0	0
Xerostomia	7(14.28%)	24(44.9%)	8(16.3%)	0	0
Acute laryngitis	5(10.2%)	22(44.9%)	0	0	0
Acute skin toxicity	18(36.7%)	13(26.5%)	3(6.12%)	0	0
Dysphagia	6(12.2%)	22(44.9%)	17(34.6%)	0	0

Table 4: Radiotherapy related toxicities

	Response	No. (49)	Percent (%)
Response Rate	-CR	32	65.30
	-PR	12	24.48
	-SD	5	10.22
		NO. (48)	**Percent (100%)**
Disease Control	Local control (CR)	32	65.30
	Loco regional failure	17	34.70

		NO. (14/48)	Percent (100%)
Site of relapse	Locoregional	11	22.9
	Distant (lung)	2	4.16
	Distant (Bone)	1	2.08

Table 5: Response details

		CR No. = 32	PR No. = 12	SD No. = 5	Test value	P-value	Sig.
Tumor volume reduction rate (%)	Median (IQR)	32.25 (26.2 – 45.7)	29.6 (9.65 – 51.05)	31.2 (31.2 – 35.8)	0.147	0.929	NS
	Range	0.6 – 63.2	0 – 82.6	4.4 – 39.5			

Table 6: Relations between TVRR and clinical outcomes

(PFS)		Total N	N of Events	Mean	SE	95% CI		Surviving proportion at		Test value	P-value	Sig.
						Lower	Upper	1 year	2 years			
	Total	49	14	30.522	1.704	27.182	33.862	89.7%	70.2%	-	-	-
Tumor volume reduction rate	<= 31.2	26	9	26.089	1.863	22.438	29.739	84.4%	66.2%	0.996	0.318	NS
	> 31.2	23	5	32.496	2.215	28.156	36.837	95.7%	74.4%			
(OS)		**Total N**	**N of Events**	**Mean**	**SE**	**95% CI**		**Surviving proportion at**		**Test value**	**P-value**	**Sig.**
						Lower	Upper	1 year	2 years			
	Total	49	11	32.438	29.580	29.580	35.297	89.8%	83.0%	-	-	-
Tumor volume reduction rate	<= 31.2	26	6	29.959	26.937	26.937	32.982	88.50%	79.70%	0.070	0.791	NS
	> 31.2	23	5	32.744	28.647	28.647	36.841	91.30%	86.50%			

Table 7: Relations between TVRR and survivals.

Survival analysis

The median (PFS) and OS have not been reached. The cumulative one-year and two-year PFS were 89.7% and 70.2%, respectively, while the cumulative one-year and two-year Os were 89.8 % and 83.0 % respectively figures (1&2).

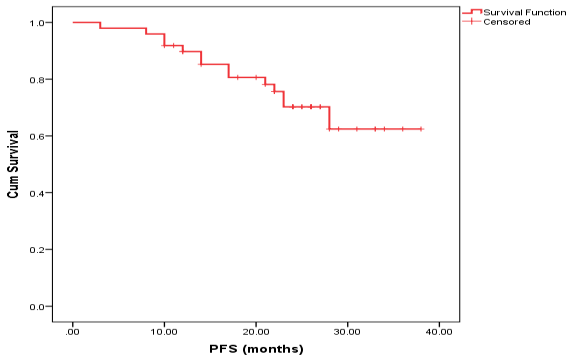

Fig. 1: progression free survival.

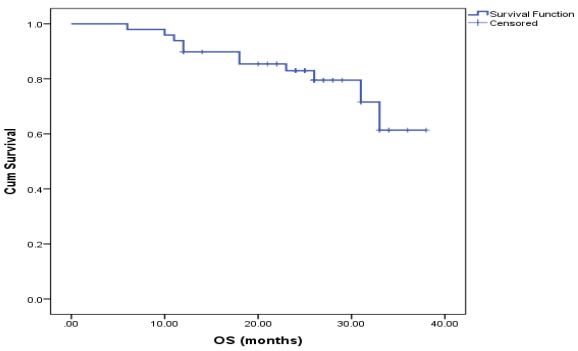

Fig. 2: Overall survival.

DISCUSSION

The majority of our patients had tumors in the Larynx (53.1%) which is matched with our national data,[6] while data published at Loyola university medical center (USA) showed the most common tumor site was oropharynx (58.2%),[5] which also matched with epidemiological data at USA that showed oropharynx is the commonest site for HNSCC.[7]

Many structures, most noticeably the primary tumor, have been demonstrated to change shape and size during radiation treatment for HNSCC. Changes in the shape and size of target structures and organs at danger during the radiation therapy process may effectively blur the dose distribution and may cause systematic uncertainties that alter the dose distribution relative to the target.[8]

According to Liu et al.9, tumor shrinkage can be detected as early as the first two weeks, with median revealed shrinkage rates varying from 3 to 16%, [9] Surcus et al.[5] found that tumor size was reduced by the end of the fourth week, with median revealed shrinkage rates ranging from7 to 48%, [5] while Loo et al.[10] discovered that the tumor size had shrunk by the end of the 7th week, with median disclosed shrinkage rates varying from 6 to 66%.[10]

In our study we found that median primary tumor volume changed from (48.3) cm^3 to (31.26) cm^3 with percentage reduction about (35.2%) at the end of 4th week.

Surcus et al.[5] attempted to link TVRR to clinical outcomes in their study and were willing to show statistically significant differences in DFS (8.9 months vs 17.5%, respectively) and OS (14.2 months vs 21.4 respectively) for patients with TVRR 35.2 % and TVRR > 35.2 %. [5]

Lee et al.[11] examined the RT registers of 59 oropharyngeal cancer patients who underwent a mid-RT scan to create an adaptive plan and discovered that patients with TVRR > 35% had significantly better 3-year loco regional control than those with TVRR 35% (94.4% versus 72.4%, respectively).[11]

Yang et al.[12] compared pre-RT GTV and interval GTV produced from rescan CT during the 4th week of therapy in 152 patients with oropharyngeal and hypopharyngeal cancer and discovered that TVRR was a statistically significant diagnostic predictor for local control.[12]

In our study, we found that the median range of tumor volume decrease rate (was 31.2 %) and by correlating TVRR with clinical outcomes our results showed no statistically significant differences for patients with TVRR 32.25% and TVRR >32.25% in two year DFS (66.2% vs 74.4%) respectively and two years OS (79.7% vs 86.5%) respectively.

When it comes to OARs, the parotid glands are especially important because their radio sensitivity is well defined, leading to a reduction in salivary output at a reduced dosage of radiation, as well as xerostomia and a lower quality of life.[13]

Eisbruch and colleagues found that even a low dosage of 26 Gy to the parotid glands could result in irreversible xerostomia. With the introduction of IMRT, therapy plans could be designed to avoid the parotid glands while still conforming to the target as well as providing sufficient coverage.[14] Even so, not all patients with excellent parotid sparing on therapy planning have excellent xerostomia rates, as 38% of patients who received IMRT in PARSPORT I and 21% in PARSPORT II had grade 2 or larger xerostomia by month 12.[15]

According to Capelle et al.[16], the average volume of the parotids shrieked during radiation therapy. The average volume of the parotids had decreased by as much as 14.7, 37, and 48% by the end of weeks 2, 4, and 7, implying that the given dosages could be much higher than anticipated by the original plan. [16]

Surcus et al.[5] discovered that the median dose reduction to the ipsilateral and contralateral parotids was 6.2% and 2.5%, respectively, in his study at Loyola University Medical Center.[5]

In our research, we discovered that the median mean ipsilateral parotid volume shrank during adaptation up to (13.62%) and the median dose reduced up to (3.86%). While the contralateral parotid volume shrank by up to (17.68%), the median dose was reduced by (5.32%).

The spinal cord is an important area of study because hot spots can form during radiation therapy. However, Capelle et al.[16] do not report any significant increases in the maximum dose during radiation therapy and Wu et al.[17] also noting no change in D max of spinal cord through the course radiotherapy. [16,17]

According to Loo et al.[10], the volume and position of the spinal cord have not been shown to change during radiation therapy, which might explain why changes in dosimetric in the spinal cord are not as coherent or profound.[10]

Even so, the dose variability in studies which do report extra dosages to the spinal cord could be quite high, with one finding a range of 0.2–15.4 Gy rise in the spinal cord peak dose (Hansen et al., 2006) and another finding 2.1–9.9 Gy, respectively. [18,19]

Surcus et al.[5] reported in their study that the median dose decrease to D max of the spinal cord was reduced by 4.5% in 51 patients with advanced neck and head cancers managed with simultaneous chemoradiation with adaptation at a median dosage of 37.8 Gy.[5]

In our study we found that the median reduction in D max of spinal cord through the course of radiotherapy was (3.5%).

The brain stem, like the spinal cord, is of interest because hot spots could be created during radiation therapy, exceeding traditional dosimetric restrictions that have been selected to keep brainstem necrosis rates low. When (D max dosage < 54 Gy) is exceeded during radiation therapy, Hansen et al.[18] recommend re-planning.

Capelle et al.[16] report no significant increases in the higher dosage over the course of radiation therapy, and Wu et al.[17] also note no change in the D max of the brain stem through the course of radiotherapy. [16,17]

Even so, in the studies which do disclose extra doses to the brain stem, the dosage variance could be quite high, with one study finding a range of 0.6–8.1 Gy increase in the brain stem max dose by Hansen et al.18, as well as 1.6–5.9 Gy by Chitapanarux et al.[19] and (4.5%) in another. [5,18,19]

In our study we found that the median reduction in D max of brain stem through the course of radiotherapy was (5.28%).

CONCLUSION

Adaptive radiation therapy helps in improving tumor coverage, decreasing dosages to organs in danger, and subsequently minimizing the expected toxicity.

REFERENCES

1. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, Morrison W, Glisson B, Trotti A, Ridge JA, Thorstad W, Wagner H, Ensley JF, Cooper JS. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. 2013 Mar 1;31(7):845-52. doi: 10.1200/JCO.2012.43.6097. Epub 2012 Nov 26. PMID: 23182993; PMCID: PMC3577950.
2. Verbakel WF, Cuijpers JP, Hoffmans D, Bieker M, Slotman BJ, Senan S. Volumetric intensity-modulated arc therapy vs. conventional IMRT in head-and-neck cancer: a comparative planning and dosimetric study. *Int J Radiat Oncol Biol Phys*. 2009 May 1;74(1):252-9. doi: 10.1016/j.ijrobp.2008.12.033. PMID: 19362244.
3. Mali SB. Adaptive Radiotherapy for Head Neck Cancer. *J Maxillofac Oral Surg*. 2016 Dec;15(4):549-554. doi: 10.1007/s12663-016-0881-y. Epub 2016 Feb 22. PMID: 27833352; PMCID: PMC5083691.
4. Chen AM, Daly ME, Cui J, Mathai M, Benedict S, Purdy JA. Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning. *Head Neck*. 2014 Nov;36(11):1541-6. doi: 10.1002/hed.23477. Epub 2014 Jan 22. PMID: 23996502.
5. Surucu M, Shah KK, Roeske JC, Choi M, Small W Jr, Emami B. Adaptive Radiotherapy for Head and Neck Cancer. *Technol Cancer Res Treat*. 2017 Apr;16(2):218-23. doi: 10.1177/1533034616662165. Epub 2016 Aug 19. PMID: 27502958; PMCID: PMC5616033.
6. Ibrahim, A. S., Khaled, H. M., Mikhail, N. N., Baraka, H., & Kamel, H. (Cancer Incidence in Egypt: Results of the National Population-Based Cancer Registry Program. *In Journal of Cancer Epidemiology*,2014 (Vol. 2014, pp. 1–18).
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020 Jan;70(1):7-30. doi: 10.3322/caac.21590. Epub 2020 Jan 8. PMID: 31912902.
8. Herk, Marcel & Remeijer, Peter & Rasch, Coen & Lebesque, Joos. . The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. *International journal of radiation oncology, biology, physics*.2000; 47. 1121-35. 10.1016/S0360-3016(00)00518-6.
9. Liu Q, Liang J, Zhou D, Krauss DJ, Chen PY, Yan D. Dosimetric Evaluation of Incorporating Patient Geometric Variations Into Adaptive Plan Optimization Through Probabilistic Treatment Planning in Head and Neck Cancers. *Int J Radiat Oncol Biol Phys*. 2018 Jul 15;101(4):985-97. doi: 10.1016/j.ijrobp.2018.03.062. Epub 2018 Apr 5. PMID: 29976511.
10. Loo H, Fairfoul J, Chakrabarti A, Dean JC, Benson RJ, Jefferies SJ, Burnet NG. Tumour shrinkage and contour change during radiotherapy increase the dose to organs at risk but not the target volumes for head and neck cancer patients treated on the TomoTherapy HiArt™ system. *Clin Oncol (R Coll Radiol)*. 2011 Feb;23(1):40-7. doi: 10.1016/j.clon.2010.09.003. Epub 2010 Oct 6. PMID: 20926268.
11. Lee H, Ahn YC, Oh D, Nam H, Kim YI, Park SY. Tumor volume reduction rate measured during adaptive definitive radiation therapy as a potential prognosticator of locoregional control in patients with oropharyngeal cancer. *Head Neck*. 2014 Apr;36(4):499-504. doi: 10.1002/hed.23328. Epub 2013 Jun 18. PMID: 23780633.
12. Yang SN, Liao CY, Chen SW, Liang JA, Tsai MH, Hua CH, Lin FJ. Clinical implications of the tumor volume reduction rate in head-and-neck cancer during definitive intensity-modulated radiotherapy for organ preservation. *Int J Radiat Oncol Biol Phys*. 2011 Mar 15;79(4):1096-103. doi: 10.1016/j.ijrobp.2009.12.055. Epub 2010 Jun 3. PMID: 20605362.
13. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. *Int J Radiat Oncol Biol Phys*. 2003 Sep 1;57(1):61-70. doi: 10.1016/s0360-3016(03)00361-4. PMID: 12909216.
14. Eisbruch A, Marsh LH, Martel MK, Ship JA, Ten Haken R, Pu AT, Fraass BA, Lichter AS. Comprehensive irradiation of head and neck cancer using conformal multisegmental fields: assessment of target coverage and noninvolved tissue sparing. *Int J Radiat Oncol Biol Phys*. 1998 Jun 1;41(3):559-68. doi: 10.1016/s0360-3016(98)00082-0. PMID: 9635702.
15. Miah AB, Schick U, Bhide SA, Guerrero-Urbano MT, Clark CH, Bidmead AM, Bodla S, Del Rosario L, Thway K, Wilson P, Newbold KL, Harrington KJ, Nutting CM. A phase II trial of induction chemotherapy and chemo-IMRT for head and neck squamous cell cancers at risk of bilateral nodal spread: the application of a bilateral superficial lobe

parotid-sparing IMRT technique and treatment outcomes. *Br J Cancer*. 2015 Jan 6;112(1):32-8. doi: 10.1038/bjc.2014.553. Epub 2014 Dec 4. PMID: 25474250; PMCID: PMC4453605.

16. Capelle L, Mackenzie M, Field C, Parliament M, Ghosh S, Scrimger R. Adaptive radiotherapy using helical tomotherapy for head and neck cancer in definitive and postoperative settings: initial results. *Clin Oncol (R Coll Radiol)*. 2012 Apr;24(3):208-15. doi: 10.1016/j.clon.2011.11.005. Epub 2011 Dec 22. PMID: 22196796.

17. Wu Q, Chi Y, Chen PY, Krauss DJ, Yan D, Martinez A. Adaptive replanning strategies accounting for shrinkage in head and neck IMRT. *Int J Radiat Oncol Biol Phys.* 2009 Nov 1;75(3):924-32. doi: 10.1016/j.ijrobp.2009.04.047. PMID: 19801104.

18. Hansen EK, Bucci MK, Quivey JM, Weinberg V, Xia P. Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2006 Feb 1;64(2):355-62. doi: 10.1016/j.ijrobp.2005.07.957. Epub 2005 Oct 26. PMID: 16256277.

19. Chitapanarux I, Chomprasert K, Nobnaop W, Wanwilairat S, Tharavichitkul E, Jakrabhandu S, Onchan W, Traisathit P, Van Gestel D. A dosimetric comparison of two-phase adaptive intensity-modulated radiotherapy for locally advanced nasopharyngeal cancer. *J Radiat Res*. 2015 May;56(3):529-38. doi: 10.1093/jrr/rru119. Epub 2015 Feb 8. PMID: 25666189; PMCID: PMC4426913.