ORIGINAL ARTICLE

Head and Neck Cancer a Single Institution Experience: King Abdulaziz University

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Abstract

The purpose of this study is to assess the loco-regional control and overall survival in head and neck cancer patients, as well as evaluate the clinical benefit of intensity-modulated radiotherapy implemented in 2011 at our Hospital. Data of 117 patients between 2007 and 2014 was reviewed retrospectively. Cumulative survival and disease control rates were calculated by Kaplan-Meier product-limit actuarial method. Loco-regional control and survival rates for intensity modulated and three-dimensional conformal radiotherapy were compared by a logistic regression test. After a median follow-up of 12 months, 53 (51%) patients who underwent radical radiotherapy were free of disease, 43 (42%) with disease, and seven (7%) unknown. During this time, 31 (26%) patients died from the disease. Using actuarial estimates for the two-year follow-up, this study found that significant gains in survival were obtained by switching treatment modalities. The benchmarking gives reassurance that our results are comparable to the best clinical practices internationally.

Keywords

Head and neck cancer; Radiotherapy; Intensity modulated radiotherapy

Introduction

Head-and-neck squamous cell carcinoma (HNSCC) is the 6th leading incident cancer worldwide with more than 600,000 cases yearly and 53,600 cases diagnosed in the US in 2013 alone[1]. Males are affected significantly more than females with a ratio ranging from 2:1 to 4:1. HNSCC accounts for 3 percent of all malignancies and 12,000 are dying from the disease annually. Tobacco smoking and alcohol consumption are the predominant risk factors for HNSCC; human papilloma virus infection (for oropharynx), diet, physical activity, and nutrition also affect the risk of developing the disease[2-4]. Additionally, family history and genetic risk factors play a role in the development of head and neck cancers that is not yet well-defined[5].

In Saudi Arabia, HNSCC is ranked 11th of the highest cancer incidences reported. According to the Saudi Cancer Registry, the incidence of all head and

neck cancer sub-sites is 7% of all cancers. Nasopharynx cancer ranks first among all head and neck cancers followed by larynx, tongue, oral cavity and or pharynx.

In the Kingdom more than half of the patients present with locoregionally advanced disease at diagnosis[6,7]; the treatment of which remains a clinical challenge that has to be refined and individualized for every case depending on several factors (age at diagnosis, primary disease stage, medical condition and organ function).

Surgery, radiotherapy and chemotherapy are the core treatment modalities for head and neck cancer in general. Radiotherapy and chemotherapy are fundamental parts of the management of patients in the adjuvant settings[8] or as a radical treatment for non-resectable cancers and for organ function preservation, for example the larynx and oropharynx. The benefit of chemo-radiation on local control (LC) and overall survival (OS) is evidently documented in the literature[9]. Moreover, the use of new techniques like intensity-modulated radiotherapy (IMRT), tomotherapy, altered fractionation and concomitant chemotherapy improved the outcomes of treatment[10,11]. The utilization of IMRT has been adopted and utilized in our department since August 2011 for all head and neck cancer patients. With IMRT, the high dose areas are sculpted around the target volumes, with steep dose fall off immediately outside these regions, consequently allowing for highly conformal radiation dose delivery. The expedient use of IMRT significantly decreases toxicity and could possibly increase locoregional control (LRC) through important progress in the nonsurgical treatment of advanced HNSCC that has been evident in recent years[12].

The purpose of this study is to present our experience in head and neck cancer at King Abdulaziz University Hospital and compare it to the published data.

Method

Patients

Between May 2007 and August 2015, 117 HNSSC patients were retrospectively reviewed at King Abdulaziz University Hospital. Pediatric patients (less than 14 years) were excluded from analysis.

All patients had confirmed pathological diagnosis in our center or reviewed for diagnosis confirmation. All patients had staging for the primary disease with computed tomography (CT) scan or magnetic resonance images (MRI) depending on the treating physician according to the latest American Joint Committee on Cancer staging version. Their demographic and clinical variables, such as age at the time of diagnosis, gender, cancer type, location, T and N stage data were collected and analyzed (Table 1). The treatment intent and modality received (surgery, chemotherapy and radiation) are detailed in Table 1.

One hundred and three (88%) patients were treated for curative intent with either concurrent chemo-radiation protocol or adjuvant radiotherapy with chemotherapy if indicated. In this study only fourteen patients were treated for palliation and symptom control. Thirty-one (26%) patients were treated with primary surgery followed by adjuvant radiotherapy with either 3D or with IMRT modality. Seventy-two (64%) patients were treated with concurrent chemo-radiation for curative intent.

Radiation Therapy Treatment Protocol

The mean prescribed dose for radical treatments was 64 Gy (range 50 – 70 Gy), delivered with mean doses per fraction of 2 Gy, (range 1.8 – 2.5 Gy). For patients who underwent post-operative radiotherapy, the radiation dose was decided based on the pathological findings.

All patients who underwent complete resection with positive margins but no gross residual (R1) and or extra-capsular extension of nodal disease received 66 Gy in conventional fractionation, 2 Gy / Fraction daily 5 times per week. Patients with R0 resection at elevated risk for recurrence received 60 Gy / 30 fractions. The radiotherapy treatment field included the surgical bed, the surgical scars, neck nodes with a greater than 10–15% risk of containing subclinical disease and anatomical sites at high-risk for loco-regional recurrence, following the Radiation Therapy Oncology Group (RTOG) Atlas for target volumes contouring. When radiotherapy was used as a primary curative treatment with or without chemotherapy, radiation dose was in the range of 66-70 Gy 33-35 fractions. Target volumes were contoured on axial CT scan slices. Gross primary and nodal tumors were contoured as gross tumor volume based on clinical findings and CT imaging or MRI done prior to neo-adjuvant chemotherapy. Clinical Target Volume (CTV) consisted of computer generated 1cm expansions around each gross tumor volume respecting anatomical barriers to include areas at high risk of recurrence. The CTV also include non-dissected nodal groups with a greater than

Table 1. Patient and tumor characteristics (n = 117).

Characteristics	N (%)	IMRT (n = 45)	3D-CRT (n = 72)
Age			
Median	48	49	50
Range	16-93	21-78	16-93
Gender			
Females	38	17 (38.00%)	21 (29.00%)
Males	79	28 (62.00%)	51 (71.00%)
Primary Tumor Site			
Nasopharynx	38 (33.00%)	17 (38.00%)	21 (29.00%)
Larynx	18 (15.00%)	5 (11.00%)	13 (18.00%)
Tongue	18 (15.00%)	8 (18.00%)	10 (14.00%)
Maxilla	7 (6.00%)	3 (7.00%)	4 (6.00%)
Hypopharynx	7 (6.00%)	3 (7.00%)	4 (6.00%)
Buccal Mucosa	5 (4.00%)	3 (7.00%)	2 (3.00%)
Others	24 (21.00%)	6 (12.00%)	18 (25.00%)
Pathology			
Squamous Cell Carcinoma	74 (63.00%)	28 (62.00%)	46 (64.00%)
Undifferentiated Carcinoma	29 (25.00%)	14 (31.00%)	15 (21.00%)
Others	14 (12.00%)	3 (7.00%)	11 (15.00%)
T Classification			
T1	19 (17.00%)	8 (18.00%)	11 (15.00%)
T2	27 (23.00%)	12 (27.00%)	15 (21.00%)
T3	25 (21.00%)	5 (11.00%)	20 (28.00%)
T4	43 (37.00%)	20 (44.00%)	23 (32.00%)
Tx	3 (2.00%)	0 (0.00%)	3 (4.00%)
N Classification			
N0	40 (34.00%)	10 (22.00%)	30 (42.00%)
N1	23 (20.00%)	10 (22.00%)	13 (18.00%)
N2	42 (36.00%)	21 (47.00%)	21 (29.00%)
N3	12 (10.00%)	4 (9.00%)	8 (11.00%)
Concomitant Chemotherapy			
Yes	25 (22.00%)	18 (40.00%)	7 (9.00%)
No	88 (75.00%)	27 (60.00%)	61 (85.00%)
Unknown	4 (3.00%)	0 (0.00%)	4 (6.00%)
Complete Surgical Resection			
Yes	31 (26.00%)	14 (31.00%)	17 (24.00%)
No	86 (74.00%)	31 (69.00%)	55 (76.00%)
Radiotherapy Treatment Intent			
Radical	103 (88.00%)	44 (98.00%)	59 (82.00%)
Palliative	14 (12.00%)	1 (2.00%)	13 (18.00%)

Abbreviations: IMRT = intensity modulated radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy

10–15% risk of containing subclinical disease. Planning target volume was constructed from an automated 0.3– 0.5 cm 3D expansion of the CTV, to account for setup error and daily uncertainty. Dose limits for the critical tissue structures and plan evaluation were as defined by the RTOG-vs0225.

Chemotherapy

Twenty-five out of 117 patients received concomitant chemotherapy with radiation (Table 1). Eighteen patients in the IMRT received chemotherapy, however only eight patients received the 3D radiation modality (Table 1; shows 7 not 8).

Chemotherapy was administrated concurrently with radiation or as neo-adjuvant and adjuvant, before and after chemotherapy, respectively. In Nasopharyngeal cancer, adjuvant chemotherapy is considered the standard of care following the treatment with concurrent chemo-radiotherapy but the administration of adjuvant chemotherapy in our center was limited due to patients' poor compliance. Alternatively, we used induction chemotherapy with TPF (docetaxel, cisplatinum and 5-FU) or cisplatinum and docetaxel as they present with large disease and compression symptoms that needed urgent and fast relief. Patients with locally advanced disease were offered TPF only if the performance status was good.

Cisplatinum was administrated concurrently as radio-sensitizer at 100 mg/m^2 every 3 weeks or 30 mg/m^2 weekly. TPF is the protocol that was used for patients with nasopharyngeal cancer.

Statistical Analysis

Cumulative survival and disease control rates were calculated by Kaplan-Meier product-limit actuarial method. The closeout date for analysis was February 2015.

Locoregional control (LRC) and OS rates for IMRT and three-dimensional conformal RT (3D-CRT) were compared by a logistic regression test and a p value of < 0.05 was considered significant.

Results

The median age was 48, age range of 16-93, with 38 females and 79 males. 63% of the patients had squamous cell cancer, 25% undifferentiated, and 12% other pathology.

One-hundred-three (88%) patients received radical treatment while 14 (12%) patients were treated with palliative radiotherapy.

Mean prescribed dose for radical treatments was 64 Gy (range 50 – 70 Gy), delivered with mean dose per fraction of 2 Gy (range 1.8 – 2.5 Gy).

After a median follow-up of 12 months (range: 1-84 months), 53 (51%) patients who underwent radical RT were free of disease, 43 (42%) with disease, and seven (7%) unknown (Figs. 1, 2).

During this time, 30 (25%) patients died from the disease, 22 (19%) of them had received radical RT.

After a two-year follow-up, the actuarial estimate rates were: 70% for local control, 91% for nodal control and 90% for distant control (Fig. 3). No significant difference was found in LRC between IMRT and 3D-CRT (Fig. 4). On differential analysis, after a two- year follow-up, the actuarial estimate rates were: 70% for local control ($p = 0.54$), 91% ($p = 0.80$) for nodal control and 63% *vs.* 70% ($p = 0.27$) for LRC in IMRT, respectively 3D-CRT (Table 2, Fig. 5).

Significant differences between IMRT and 3D-CRT were found in survival (Fig. 5). The actuarial estimate rates at two years were: 87% *vs.* 73% ($p = 0.0453$) for OS and 64% *vs.* 52% ($p = 0.0421$) for disease-free survival (DFS) in IMRT, respectively 3D-CRT (Fig. 6).

Due to the small number of patients, further sub-group analysis with respect to diagnosis, age or gender was not performed.

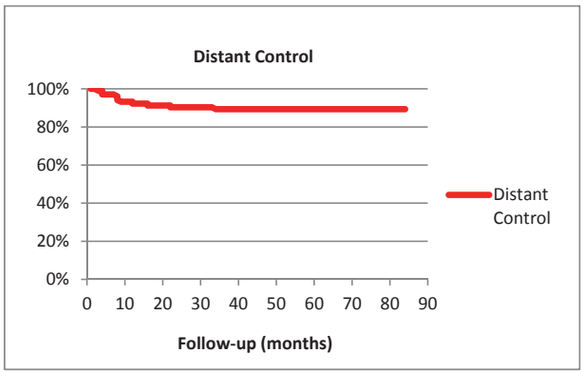

Figure 1. Distant control for all patients who received radiotherapy.

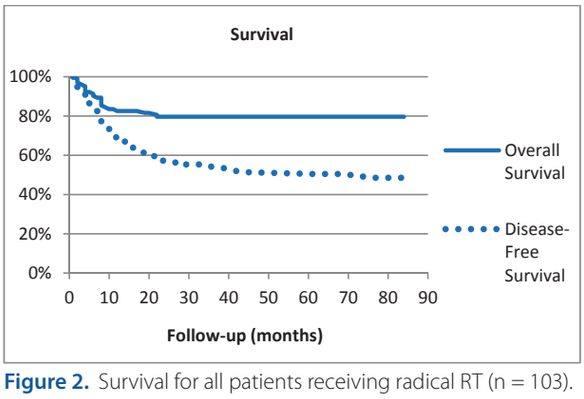

Figure 2. Survival for all patients receiving radical RT (n = 103).

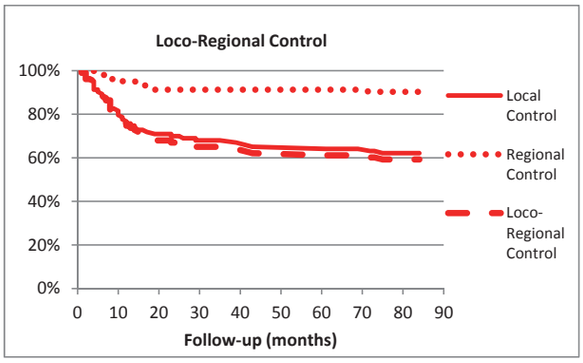

Figure 3. Disease control for all patients receiving radical RT (n = 103).

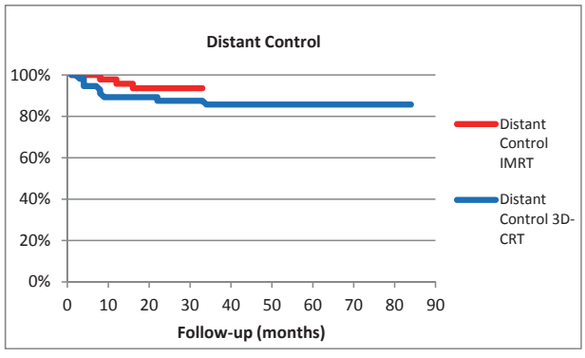

Figure 5. Comparison of distant control between intensity modulated radiotherapy (IMRT) and three dimensional radiotherapy (3D-RT).

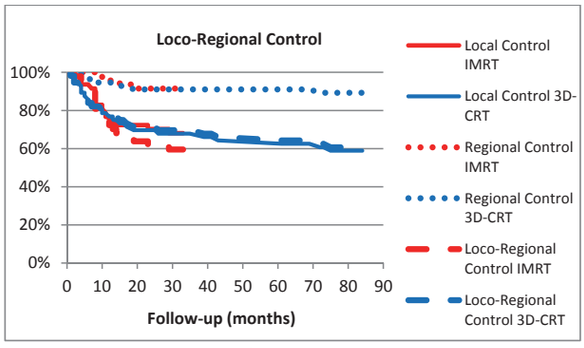

Figure 4. Comparison of disease control between intensity modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3D-CRT).

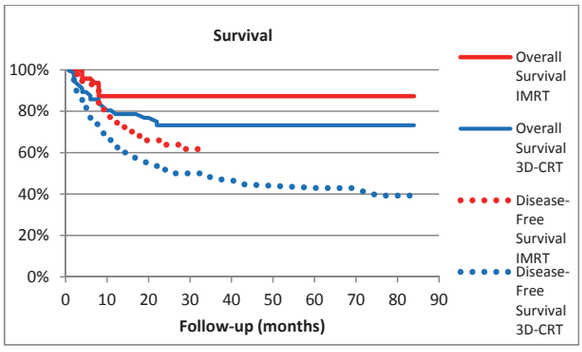

Figure 6. Comparison of survivals between intensity modulated radiotherapy (IMRT) and three-dimensional conformal RT (3D-CRT).

Table 2. Comparison of locoregional control and survival between IMRT and 3D-CRT for radical treatment (n = 103).

Characteristic	n (%)	IMRT (n = 44)	3D-CRT (n = 59)
Follow-up			
Median	12	14	13
Range	1-84	1-41	1-84
Clinical Outcome			
Free of Disease	53 (51.00%)	26 (59.00%)	27 (46.00%)
Loco-Regional Relapse	33 (32.00%)	15 (34.00%)	20 (34.00%)
Mets	10 (10.00%)	3 (7.00%)	7 (12.00%)
Died	23 (22.00%)	8 (18.00%)	15 (25.00%)
Unknown	7 (7.00%)	2 (4.00%)	5 (8.00%)

Abbreviations: IMRT = intensity modulated radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy

Discussion

In the current review, we present our experience at King Abdulaziz University Hospital, switching from three-dimensional radiotherapy (3D-RT) to IMRT. This study also reports the results of our practice for all head and neck sub-sites and compares it to the published data.

It was not unexpected to find out that the cases that received the radiotherapy as IMRT technique resulted in similar loco-regional control rates, but significantly higher survival rates, when compared to 3D-CRT. We think this observation goes with the improvement in the chemotherapy availability at the time radiation had followed the state of the art. Only 7% of the patients treated with 3D-RT, received chemotherapy in comparison to 40 % in the IMRT group. In addition the percentage of the advanced cancer were slightly higher in the 3D-RT group, (60%), and 55% in the IMRT group. Also we think is it difficult to compare the results of the two modalities as they have different patients, treatments, periods, and follow-ups.

The outcomes of the group of patients treated with IMRT are comparable to the published reports from different international centers. In this review, the two-year rates for OS, DFS, local control, nodal control, and LRC are 87%, 64%, 70%, 91% and 63%, respectively. Studer *et al.*[15]. reported their results for 280 head and neck patients treated with IMRT. Chemotherapy was given in 85%, and 71% of patients were treated with definitive and post-op radiotherapy, respectively. The two-year rates for OS, DFS, local control, and nodal control were 82%, 73%, 80%, and 87%, respectively[15]. Schoenfeld *et al.*[16] published the outcome of 100 head and neck patients treated with IMRT. All patients received definitive radiotherapy and 54% were treated concomitantly with chemotherapy. The three-year rates for OS, DFS, local control, and LRC were 71%, 77%, 87%, and 72%, respectively [16]. In 2012, Vlacich *et al.*[17] published the outcome of 150 patients of head and neck cancer treated with IMRT. All patients had advanced disease (stage III and IV) and all of them received concurrent chemotherapy, and most of the patients (67%) received induction chemotherapy. The two-year rates of OS, DFS, local recurrence-free survival, and loco-regional recurrence-free survival were 82%, 83%, 88%, and 89%, respectively[17]. Similar results are published in other reports[18,19]. Table 3 summarizes the outcomes of this review in comparison with other published data. We noticed lower rates of DFS and LRC in our review for the patients treated with IMRT, this could be due to the smaller percentage of patients (40%) who received chemotherapy, though more than half of the patients have advanced disease (T3 or N2 and higher). Also, a smaller number of patients (45 patients only) may affect the real results (Table 3).

Looking at the end outcomes, it is still reasonable and satisfying for the treating team to consider King Abdulaziz University as a leading center in the field of Head and Neck Oncology.

The last few years have seen tremendous improvement in the supportive services at our institute including nutrition, psychiatry, palliative care and social work referrals. Our prospects for the future include optimizing patients' care, improving treatment outcomes and increasing community awareness regarding the importance of early presentations and risk reduction measures.

Conclusion

Post-operative IMRT resulted in similar loco-regional control rates, but significantly higher survival rates, when compared to 3D-CRT. The results reflect the past unavailability of chemotherapy at our institute. The benchmarking gives reassurance that practice in our center is comparable to the best clinical practices internationally.

Table 3. Outcomes of different published data.

Report	No.	FU-rate	Chemotherapy %	OS%	DFS%	LC%	NC%	LRC%
Current Review	45	2Y	40%	87%	64%	70%	91%	63%
Studer *et al.*[15]	280	2Y	85 definitive 71 pos-op	82%	73%	80%	87%	N
Schoenfeld *et al.*[16]	100	3Y	54%	71%	77%	87%		72%
Vlacich *et al.*[17]	150	2Y	100%	82%	83%	88%	-	89%
Yao *et al.*[18]	150	2Y	69%	85%	-	94%	-	92%

Abbreviations: Fu = Follow up; OS = Overall survival; DFS = Disease free survival; LC = Local control; NC = Nodal control; LCR = Loco regional control

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Conflict of Interest

The authors have no conflict of interest.

Disclosure

None of the authors received any type of commercial support either in forms of compensation or financial for this study. They have no financial interest in any of the products or devices, or drugs mentioned in this article.

Ethical Approval

Obtained.

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تجربة مستشفى جامعة الملك عبدالعزيز مع أورام الرأس والرقبة

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كلية الطب، جامعة الملك عبدالعزيز و [٣]قسم الأورام، مستشفى الملك فيصل التخصصي ومركز الأبحاث
جدة - المملكة العربية السعودية

المستخلص. غرض دراستنا هو تقييم ضبط التحكم الموضعي في الورم، والبقاء على قيد الحياة في مرضى سرطان الرأس والعنق، وتقييم الفائدة السريرية للعلاج الإشعاعي متغير الكثافة الذي تم تفعيله في عام ٢٠١١ في مستشفى جامعةالملك عبدالعزيز. وتم بأثر رجعي استعراض بيانات ١١٧ مريضاً بين عامي ٢٠٠٧ و٢٠١٤. تم حساب المعدل التراكمي للبقاء على قيد الحياة ومعدلات السيطرة على الورم بواسطة كابلان ماير والطريقة الاكتوارية. وتمت مقارنة معدلات السيطرة والبقاء على قيد الحياة للعلاج المتغيرالكثافة والعلاج الإشعاعي ثلاثي الأبعاد بعد ١٢ شهراً من متوسط المتابعة. تعافى من المرضى ٥٣ (٥١٪) من المرضى الذين خضعوا للعلاج الجذري بالأشعة، و٤٣ (٤٢٪) منهم ما زالوا يعانون من المرض، ولم تعرف حالة ٧ (٧٪) منهم. خلال هذا الوقت، توفي ٣١ (٢٦٪) من المرضى. وكانت معدلات التقديرات الاكتوارية في سنتين: ٨٧٪ مقابل ٧٣٪ (٠,٠٤٥٣) للبقاء على قيد الحياة و٦٤٪ مقابل ٥٢٪ (٠,٠٤٢١) للبقاء على قيد الحياه بلا مرض للعلاج المتغيرالكثافة والثلاثي الأبعاد، على التوالي. والقياس يعطي الاطمئنان إلى أن نتائجنا قابلة للمقارنة لأفضل الممارسات السريرية على الصعيد الدولي.