Res. Oncol.
Vol. 12, No. 1, Jun. 2016:2-9

Original article

A retrospective study of reirradiation for patients with locoregional recurrent head and neck cancer: A single-institution experience

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Aim: To assess the efficacy of reirradiation in locoregionally recurrent head and neck cancer (HNC) and to describe results in our center in relation to other published data among similar group of patients.
Methods: The medical records of 28 patients with HNC who received reirradiation with or without chemotherapy for loco-regional recurrence between 2005 and 2013 were reviewed. They were evaluated for; toxicity profile, overall survival (OS) and progression free survival (PFS).
Results: The median reirradiation dose was 50 Gy (range 40-60 Gy) and median radiation cumulative dose was 119 (range 113 -120). An overall response rate was seen in 36% of patients with only 3 patients showed complete response. The median OS was 9 months with 1-and 2-year survival rates being 34.1% and 10.6%. The OS and PFS were significantly better in patients who were treated with chemotherapy concomitant with radiation and received higher radiation dose. Grade 3 mucositis and skin reactions were seen in 24 % and 14% of patients, respectively.
Conclusion: Reirradiation appears to be feasible in patients with recurrent HNC treated previously with radiation. The benefit of concurrent chemotherapy with reirradiation is expected. Our results are subject to limitations from the retrospective nature of the analysis, the relatively small number, and improper selection of patients.

Key words: Reirradiation, Recurrent head and neck cancer, Chemoradiotherapy.
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Received: 31-Aug-2016, Accepted: 1-Sep-2016

Original article

INTRODUCTION

Although head and neck cancer (HNC) is the sixth most common cancer worldwide, Egyptian studies reveal variations of incidence. In a data-base study, head and neck squamous cell carcinoma (HNSCC) constituted about 17-20% of all malignancies of El-Gharbeya Governorate Hospitals[1], while in the cancer registry of Ain Shams University constitutes about 8% of the total malignancies[2].

Patients with locally recurrent HNSCC have a poor prognosis and limited therapeutic options. Prognosis of these patients with recurrent HNC is dismal if the tumor is left untreated, with a median survival of only 5 months[3]. Locoregional recurrence occurring at rate of 20% to 30% remains the predominant site of recurrence and cause of death following treatment[4]. Salvage surgery is the preferred option if feasible and 25% to 45% of patients experience long term disease control. However, recurrent disease is often not resectable. Even in resectable cases, patients' comorbidities or refusal can be obstacles[5]. Systemic chemotherapy when used in such patients yields response rate of only 20 to 35% with median survival of 6 to 8 months with no chance at long term tumor control and usually used with palliative intent[6].

Several studies suggest that relatively long-term survival of more than 3 years may be possible with multimodality treatment incorporating reirradiation (ReRT)[4]. Concurrent ReRT and chemotherapy if feasible is an alternative strategy. Median overall survival (OS) of 10 months and a 3-year OS of 22% were reported with ReRT alone[7, 8].

Because of the radio-sensitizing activity of 5-fluorouracil and hydroxyurea and their different toxicity profile, they may be combined to irradiation of HNC[9]. Treatment of recurrent or 2nd primary HNC using concurrent ReRT with 5-fluorouracil and

hydroxyurea combination resulted in a survival rates ranging from 15% to 45% at 2 years[10, 11].

This retrospective study was carried out to assess the efficacy of ReRT in locoregionally recurrent HNC and to describe results in our center in relation to other published data among similar groups.

METHODS

Patients' selection

The medical records of 28 patients with recurrent HNC who received ReRT with or without chemotherapy for loco-regional recurrence between 2005 and 2013 were reviewed. All patients included were non-metastatic at both the initial and the second presentation. All patients had histological and /or radiological proof of loco-regional recurrence.

Pretreatment evaluation

All patients had undergone a pretreatment evaluation, including a complete history and physical examination, complete hemogram and biochemistry profile, computed tomography (CT) or magnetic resonance imaging of the head and neck region. Screening for distant metastasis was done using CT chest, abdominal CT as well as bone scan.

Treatment

All patients were first evaluated for possibility of surgical resection if feasible according to extent of disease and resectability.

A 4- 6 MV photon linear accelerator was used to deliver radiotherapy (RT) with thermoplastic immobilization. Treatment was delivered by conventional two-dimensional RT until 2007 then by three-dimensional conformal RT thereafter.

Whenever available, plans of the initial course of RT were revised to define the previously irradiated areas and maximum doses that can be given to critical structures.

The ReRT dose ranged between 40-60 Gy, 1.8-2 Gy/fraction, 5 fractions/week.

The gross tumor volume was defined radiologically and clinically, whereas the clinical target volume margin was 1 to 1.5 cm and the planning target volume was 0.5cm.

Attempts were made to deliver maximal cumulative dose to spinal cord, brain stem and optic apparatus below 50 Gy, 54 Gy and 55 Gy; respectively.

No elective treatment for adjacent sites or draining lymph nodes was given. Lymph nodes overlying the spiral cord were treated by electrons.

Radiotherapy was given concurrently with chemotherapy when possible and Eastern Cooperative Oncology Group (ECOG) performance status of patients was ≤2 with no contraindications for chemotherapy including a platinum-based regimens.

Response evaluation and follow-up

The response was assessed at 6 -8 weeks after the completion of treatment by clinical examination, CT scan and endoscopy and every 3 to 6 months thereafter. Thyroid function tests and endoscopy were done every 6 months or whenever needed.

Toxicity

Acute and late toxicities were measured according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (NCI - CTCAE)[12].

Statistics

The median follow-up was measured from the first day of ReRT to the day of last visit before analysis (June 2016) or death.

Statistical analysis was done using the SPSS version 19.0. The duration of OS and progression free survival (PFS) were calculated from first day of starting treatment (re-irradiation course). Overall survival was measured from the first day of retreatment till death of any cause or last patient follow up contact. Progression free survival was calculated from the first day of ReRT until the first evidence of progression (locoregional progression or distant failure) or death from any cause.

Survival analysis was carried out using the Kaplan-Meier method.

RESULTS

Patient characteristics

Characteristics of study patients are outlined in table 1. The median patients' age was 57 and the majority of patients (75%) were males. Half of the patients had loco-regional recurrences (primary site and lymph nodes). All patients had squamous cell carcinoma. The majority of patients (93%) had locally advanced disease (stage III-IV) at initial presentation and initial treatment consisted of concomitant chemo-radiotherapy in 39%, surgery followed by RT ± chemotherapy in 21%, induction followed by concomitant chemo-radiotherapy in 21% and RT as a single modality in 18%. The median disease- free-interval from initial treatment to recurrence was 10 months (range 5 -31 months).

Salvage treatment and radiotherapy

None of the patients underwent surgery before ReRT course either because of tumor unresectability or due to poor general condition.

Details of RT are shown in table 2. The median dose of prior radiation was 70 Gy (range: 58- 70 Gy) as most of the patients received dose of 70 Gy. Prior radiation was given using two-dimensional RT technique in 18 patients (64%). The median duration between initial RT and ReRT was 12 months (range: 7-33 months). Most patients did not receive chemotherapy with ReRT (21 patients, 75%), while 4 patients (14%) and 2 patients (7%) received concurrent weekly carboplatin and cisplatin; respectively. The median ReRT dose was 50 Gy (range: 40 -60 Gy) and 54% of patients received RT dose ≥50 Gy. Reirradiation was performed using three-dimensional technique in 15 patients (54%) and two-dimensional technique in the remaining 13 patients. All patients received conventional fractionation protocol. It was found that the ReRT dose was influenced by the interval between initial RT and ReRT as shown in table 3. Higher ReRT dose was given (>50 Gy) if the interval between the initial RT course and the ReRT course was >12 months. It was found to be statistically-significant (p<0.001).

Response

The median follow-up period was 11 months (range: 247- months). The clinical overall response rate (complete remission + partial remission) was seen in 10 (36%) patients, of which 3 patients (11%) had achieved complete remission after completion of treatment. Ten patients (36%) had stable disease. At time of analysis, twenty patients (71%) had locoregional failure, five (18%) had distant failure and three (11%) had persistent disease.

Survival

The OS at 1-year and 2-year were 34% and 11%, respectively, with a median survival of 9 months. The PFS rate at 1-year was 20%. No patient was progression free at 2 years. The median PFS was 6 months. Figures 1 and 2 display the Kaplan–Meier survival curves of PFS and OS, respectively.

Univariate analysis was used to test for factors which were predictive of OS and PFS. The factors tested for significance were ECOG performance status, ReRT dose, time from initial radiation and addition of concomitant chemotherapy table 4.

Addition of chemotherapy, increasing ReRT dose and increase time interval before ReRT correlated with better OS and PFS. Meanwhile, better ECOG performance status associated with better OS.

Toxicity

Recorded acute and late toxicities are illustrated in table 5.

Details of acute toxicities were recorded in 21 /28 of cases. They mainly consisted of mucositis and skin reactions. Grade 3- 4 mucositis was documented in 5/ 21 patients (24%), while 3 /21 (14%) patients suffered from grade 3 skin reactions.

Late toxicities were well documented in 1928/ patients. Grade 3-4 trismus and subcutaneous fibrosis were seen in 16% (3 /19) and 37% (7/ 19), respectively.

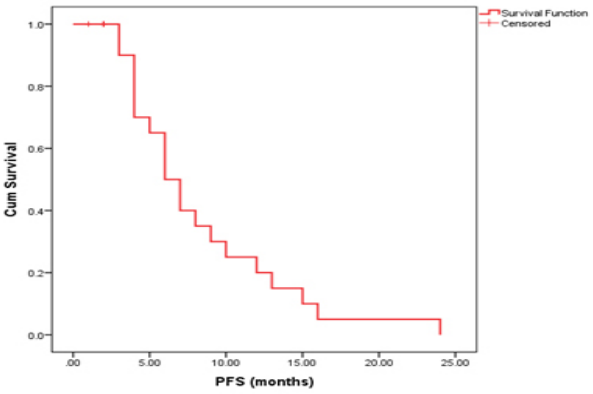

Figure 1: Kaplan–Meier survival curve of progression free survival

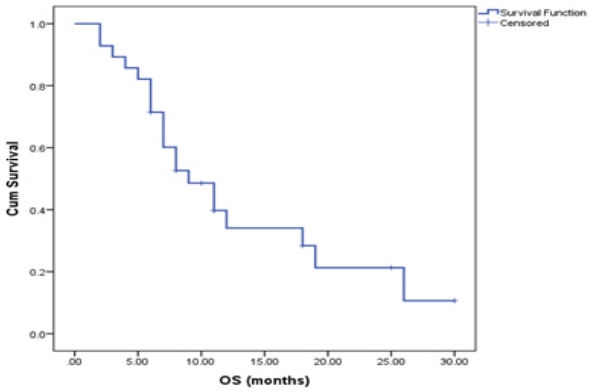

Figure 2: Kaplan–Meier survival curve of overall survival

Table 1: Patients' characteristics

Characteristic	***n.***	**%**
Age in years		
Median (range)	57 (39-75)	
Gender		
Male	7	25
Female	21	75
Initial Primary Site		
Larynx	13	47
Hypopharynx	4	14
Oroopharynx	3	11
Nasopharynx	2	7
Oral cavity	2	7
Sinonasal	2	7
Metastases of unknown origin to cervical lymph nodes	2	7
Initial Stage		
Stage I-II	2	7
Stage III-IV	26	93
Initial Treatment		
Radiotherapy alone	5	18
Surgery followed by radiotherapy ± chemotherapy	6	21
Concomitant chemo-radiotherapy	11	39
Induction chemotherapy then concomitant chemo-radiotherapy	6	21
Initial radiotherapy dose (Gy)		
60	7	25
≥ 60	21	75
Median	70	
Response to Initial Treatment		
Complete response	16	57
Partial response	12	43
Site of Recurrence		
Local only	10	36
Nodal only	4	14
Both	14	50
Disease-free-interval from initial treatment to recurrence (months)		
Median (range)	10 (5-31)	

Table 2: Reirradiation details.

	n.	%
Duration between initial radiotherapy and reirradiation (months)		
Median (range)	12 (7-33)	
≤12 months	15	54
>12 months	13	46
Dose (Gy)		
Median (range)		
≥ 50	15	54
< 50	13	46
Radiotherapy technique		
Two-dimensional	13	46
Three-dimensional	15	54
Chemotherapy		
Yes	7	25
No	21	75

Table 3: Correlation between reirradiation dose and time interval

Time interval	**Dose < 50**		**Dose ≥ 50**		**Chi-square test**	
	n.	**%**	***n.***	**%**	χ^2	***p*-value**
≤12 months	12	92.3	3	20.0		
> 12 months	1	7.7	12	80.0	14.64	<0.001
Total	13	100	15	100		

Table 4: Univariate analysis of survival

	N	**OS (months)**			**P-value**	**PFS (months)**			**P-value**
		Median	**SE**	**95% CI**		**Median**	**SE**	**95% CI**	
Reirradiation dose									
< 50	13	6	0.899	4.24 – 7.76	< 0.001	4	0.577	2.87 – 5.13	0.001
≥ 50	15	18	4.7	8.79 – 27.21		8	1.871	4.33 – 11.67	
Time interval									
≤ 12 months	15	6	0.644	4.74 – 7.26	< 0.001	5	1.309	2.43 – 7.57	0.007
> 12 months	13	19	1.197	16.65 – 21.35		9	1.797	5.48 – 12.52	
ECOG									
≤ 2	18	18	4.647	8.89 – 27.11	< 0.001	7	2.000	3.08 – 10.92	0.117
3	10	5	1.581	1.9 – 8.1		4	-	-	
Chemotherapy									
No	21	8	0.858	6.32 – 9.68	0.004	5	0.935	3.17 – 6.83	<0.001
Yes	7	26	6.06	14.12 – 37.88		13	3.062	7 – 19	

Table 5: Toxicity profile.

	G I-II		G III-IV	
	n	%	n	%
Acute toxicities (n = 21)				
Mucositis	15	71	5	24
Skin	10	48	3	14
Dysphagia	3	5	0	0
Late toxicities (n = 19)				
Subcutaneous fibrosis	9	47	7	37
Trismus	4	21	3	16

DISCUSSION

Recurrent HNSCC in previously radiated regions present a unique challenge to the treatment. Locoregional recurrence usually has a poor prognosis with a median survival of approximately 6 months with best supportive care alone[13].

Surgery is the mainstay and the standard of treatment for locoregional head and neck recurrence with 5 year survival rates ranging from 23% to 55%. But it is feasible in only 15 -20% of patients with resectable tumors and sufficiently good health status [14].

In this group of patients, the systemic chemotherapy role is palliative when used alone. When used alone, platinum-based chemotherapy was associated with a 5-year survival rate of only 4% among patients with recurrent/metastatic HNSCC[15].

Reirradiation alone or combined with chemotherapy is a valid option and seems promising.

The current study presents the outcome of 28 patients who received ReRT with or without chemotherapy. At the completion of protocol therapy, patients were assessed for treatment response. The response rate was 36%, of which 11% (3 /28) had achieved a CR after completion of treatment. Most of previous studies, however, documented better outcomes with response rates of 41- 85%[16 - 18].

In comparison to other ReRT series the inferior treatment results obtained in our study might be due to many reasons/factors. First, all patients did not do salvage surgery because of bulky/unresectable cancer, which in consequence decreased the effect of radiation therapy due to increased tumor burden and hypoxic cells. Furthermore, most of patients did not receive systemic chemotherapy concomitant with irradiation either due to organ dysfunction or comorbidity. Radiotherapy effect is intensified when chemotherapy is administered concurrently due to synergism or radio-sensitization[19].

In our group of patients, we found a median OS of 9 months and OS of 10 % at 2 years, while PFS at 1 year was 20%. At 2 years all patients had progressed.

The results of the current study are consistent with those of a larger experience from the Institute Gustav Roussy, in which 169 patients received ReRT ± chemotherapy. Depending on the regimen of treatment, 2-year OS in that study ranged from 10% to 25% and 2-year disease-free-survival from 3% to 14%. The median survival of patients was dismal ranging from 10 to 11 months[20].

In a retrospective study, *Janssen et al* reviewed 55 patients who received ReRT, of which 47% received chemotherapy[21]. They reported 2 years OS of 16% on the group of patients who received RT alone, while patients who received concomitant CRT showed 2-years OS of 30%. Alike, in our study only 25% (7 patients) received concomitant chemotherapy and showed median OS of 26 months. On contrary, patients who didn't receive chemotherapy (21 patients) showed median OS of 8 months.

In a prospective trial, *Berger, et al* [22] tried different radiation schedules with different ReRT total dose either TD 40 Gy or TD 49.6 Gy on a total of 57 patients. Concomitant with chemotherapy (cisplatin/docetaxel) they reported 2 year OS of 16% in 40 Gy group and OS 31% in 49.6 Gy group, denoting a better outcome with a total ReRT dose of 50 Gy or more. Same results were recorded in many other trials[16, 20, 23, 24].

All patients reviewed in our study did not do salvage surgery before ReRT either due to unresectable tumors or they were unfit for surgery which explain the low OS and PFS figures. Similarly, *Salama et al.* showed that surgery prior to ReRT predicted independently better OS and locoregional PFS [24]. Other studies confirmed the better OS associated with surgical resection before ReRT[20, 26, 27].

Moreover, our results of PFS and OS are far less than the results reported by *Sher et al*[28] where 35 patients with recurrent HNC treated with continuous course ReRT, while using platinum based chemotherapy and an intensity-modulated RT technique. The actuarial 2-year survival was 48% and a median OS of 1.9 years.

Al-Wassia et al[29] reported the McGill university experience of 27 patients with recurrent HNC who underwent ReRT with concomitant chemotherapy / targeted therapy in 77% of patients. An intensity-modulated RT technique was used in 55% of patients. The actuarial OS rate at 2 years was 59% and PFS was 52% respectively.

These good results in the aforementioned trials can be attributed to the use of intensity-modulated RT, which allowed the delivery of ReRT in a more conformal fashion, minimizing acute toxicities and reducing treatment interruptions, which allow delivery of radical doses to the tumor. Moreover, the majority of patients enrolled in these trials have received concomitant chemotherapy.

Noteworthy, these previous favorable results may be the reflection of good patient's selection criteria including good performance status, in contrary to our study.

In our study, analysis of toxicity revealed that up to 24% of the patients have acute mucositis (grade 3) and skin reactions recorded in 14% of the patients. These results were comparable to that reported by *Kakria et al*[30], whereas 29% of patients have acute toxicity. On contrary, *Nagar et al*[16] reported a rate of acute (grade 3) mucositis (10%) and skin reactions (7%), these lower rates could be attributed to the lower doses of RT used in their study.

In our study, severe late toxicity (grade 3) in the form of subcutaneous fibrosis and trismus were seen in 37% and 16%, respectively. This is not far from that reported in other studies[32].

The rate of severe toxicity denotes the need to improve therapeutic efficacy and patient selection criteria.

Riaz et al[33] determined prognostic factors for loco-regional control and OS, whereas they formulated a nomogram to help clinicians in selection of ReRT candidates. Many prognostic factors associate with better outcome including; recurrence stage (small volume of disease), non-oral cavity subsite, absent organ dysfunction, salvage surgery and dose >50 Gy. Our study comes favorably with their results whereas the group of patients who received ReRT dose> 50 had better median OS and PFS of 18 and 8 months, respectively. Meanwhile, the group of patients with prolonged time interval "i.e.>12 months from primary treatment" and ReRT showed better outcomes with median OS and PFS of 19 and 9 months, respectively.

On the contrary the performance status, which usually reflects organ dysfunction, has no effect on PFS in our study, which can be due to small number of patients.

CONCLUSIONS

Though the results from this study are subject to limitations from the retrospective nature of the analysis and the relatively small number, we can conclude the importance of appropriate patients' selection for ReRT. Better ReRT outcome is expected among those with less comorbidities and toxicities secondary to initial RT.

Other predictor factors that should be taken in account are the small tumor size and longer period since previous irradiation, keeping in mind that salvage surgery whenever possible is the best option. Also new RT techniques like intensity-modulated RT are recommended as they may improve outcomes in terms of local control and toxicity and allow delivery of radiation dose ≥ 60 Gy.

Finally, the benefit of concurrent chemotherapy with ReRT is expected.

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