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Head and neck squamous cell carcinoma: Mansoura 10 years experience

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ABSTRACT

Head and neck (H&N) cancers are the sixth most prevalent cancers in the world with squamous cell carcinoma (SCC) constituting around 90% of it. One hundred and eighty eight patients with H&N SCC were treated at Mansoura University Hospital in the period from January 1990 to December 1999 inclusive. For those 188 cases we analyzed their clinico-epidemiologic data, survival, prognostic factors, patterns of failure and toxicity of therapy. Unfortunately 75.5% of the cases presented in advanced stages. The median event-free survival duration was 14 months, while the median overall survival duration was 22 months. The 5-year event-free survival and overall survival were 45% and 53%, respectively. On multivariate analysis for event-free survival, only performance status and grade were significant ($p \leq 0.05$). On the other hand multivariate analysis for overall survival found only performance status and stage to be significant ($p \leq 0.05$). Local failure exceeded in incidence both nodal and distant failure. The majority of our H&N SCC cases presented with advanced stages of the disease. Controlling risk factors and early cancer detection are needed to decrease the incidence and increase the survival of such tumors.[Turk J Cancer 2005;35(2):70-80].

KEY WORDS

Head and neck, cancer, retrospective, radiotherapy

INTRODUCTION

In the year 2000, cancer accounted for 7 million deaths (13% of the total mortality) all over the world. Moreover, more than 10 million new cancer cases were reported. It is worth to note that more than 60% of cancer deaths and approximately half of the new cases occurred in developing countries (1).

Head and neck cancer are the sixth most prevalent cancer in the world, with a global yearly incidence of 500,000 (2).

Squamous cell carcinoma constitutes 90% of all head and neck cancers and it predominates in males. Risk factors such as cigarette smoking and alcohol intake are well established (3).

Treatment decisions are guided by clinico-pathologic factors such as age and stage. Although useful, those factors alone do not provide all the information concerning the aggressiveness of the tumor (4). Consequently, biologic markers that can provide prognostically useful information are being identified (5).

Radiotherapy or surgery alone can be considered as the standard treatment modality for patients having early head and neck squamous cell carcinoma, whereas radiotherapy in combination with surgery and/or chemotherapy are used for those with locally advanced tumors (6). When conventionally fractionated radiotherapy is used, long-term tumor control can be achieved in less than 30% of patients with

advanced head and neck carcinomas. To improve local control, altered fractionations like accelerated hyperfractionation have been tried (7). Moreover polychemotherapy regimens used concomitantly with radiotherapy have yielded more satisfactory results (8).

The purpose of this study is to characterize head and neck squamous cell carcinomas in our region with regard to the clinico-pathologic characteristics, prognostic factors, response to treatment toxicity and survival.

MATERIALS AND METHODS

From January 1990 to December 1999 inclusive, 302 cases of head and neck squamous cell carcinomas were registered at the clinical Oncology and Nuclear Medicine Department of Mansoura University Hospital. However, only 188 cases were included in this study as they had reliable complete data.

Patient characteristics included age, sex, date of diagnosis, site and size of the tumor and performance status according to the WHO scale reported by Miller et al (9).

Staging procedures included physical examination, endoscopy, computerized tomography of the head and neck (CT) or magnetic resonance imaging (MRI). Plain X-ray of the chest and abdominal ultrasound were done to exclude metastasis. The tumors were staged according to the UICC TNM classification (10).

Treatment modalities

One hundred and eight cases (57%) received radical radiotherapy due to inaccessibility in 42 cases (39%), advanced tumors beyond non-mutilating surgeries in 35 cases (32%) and function preservation in 31 operable cases (29%). Eight advanced cases received concomitant chemoradiotherapy.

Eighty operable cases received radiotherapy after surgery either due to advanced stages in 70 cases (87.5%) or due to positive safety margins in the postoperative pathology report of early tumors in 10 cases (12.5%). Surgeries done included total laryngectomy (80%), subtotal laryngectomy (7.5%), partial laryngopharyngectomy (3.7%), partial glossectomy (3.7%), total glossectomy (2.5%) and radical maxillectomy (2.5%). Different extents of neck dissections according to the nodal stage were done.

Radiotherapy technique

The simulator was used for planning and immobilizing masks were used for reproducibility of the sittings. Two parallel opposing neck fields including the tumor plus the surrounding tissues and the draining lymphatics were defined in most of the cases. After a tumor dose of 45 Gy, the posterior margin of lateral border was brought anteriorly excluding the spinal cord and then the rest of the dose of radiotherapy was given. In the case of clinically positive lymph nodes, an electron beam was used to increase the dose to the posterior cervical nodes after 45 Gy without allowing further dose to the spinal cord when no neck dissection was done.

After a radical dose of 65 Gy had been delivered, the portal were concentrically reduced to deliver to the gross volume a dose reaching 70-75 Gy according to T stage. The lower neck (usually below the level of the thyroid notch) was treated with an anterior portal giving 50 Gy given dose. If no palpable lymph nodes are present at or near the midline, a 5 half-value layer 1.5 to 2 cm wide midline block was used to shield the larynx and spinal cord. This block was not used in cases of laryngeal and hypopharyngeal tumors.

Exceptions of field arrangement were in cases of T1 and T2 glottic tumors, in which small portals covering only the primary lesions were used and the cervical lymph node chains were not electively treated and after radical maxillectomy for maxillary carcinomas. In the latter, an anterior portal with one or two posteriorly tilted lateral portal (frequently wedged) was applied. The target volume included the entire nasal cavity, the ethmoid-sphenoid complex and the medial contralateral orbit. The mandible and tongue were displaced out of the field by a tongue blade and a cork.

Radiotherapy doses

In radical radiotherapy the dose depended on various factors like the stage. Generally doses ranging from 65 Gy to 75 Gy had been used. The postoperative radiotherapy dose was 50 Gy in cases of N0 tumors and negative margins. Doses ranging from 60-65 Gy were delivered in cases of microscopic or macroscopic residual.

Fractionation

Two grays given per fraction, one fraction per day and five per fractions per week had been the applied fractionation scheme.

The response to treatment in the cases managed by radical radiotherapy was assessed according to WHO criteria (9).

Toxicity

Toxicity was graded using the WHO scale (11).

Follow up

All patients underwent repeated clinical examination during the radiotherapy to assess acute toxicity reaction. A follow up every 3 months was done by complete physical examination and CT scan of the head and neck region during the first year. During the following years longer spacing between the follow up visits was done. Metastatic work up including chest x-ray and abdominal ultrasound were performed if the patients developed significant related symptoms.

Statistics

Statistical analysis was done using the Statistical Package for Social Science program version 10.0 (1999).

Event-free survival was calculated from the date of registration in our department to the date of the first documentation of relapse, progression or metastasis, while overall survival was calculated from the date of registration in our department to the date of death or the last follow up. The Kaplan Meier's method was used for the calculation of survival curves.

Univariate and multivariate statistical analysis were performed according to the multiple stepwise regression analysis.

Chi-square test with Yates correction was used to detect statistical differences in proportions. A p value of ≤0.05 was considered significant

RESULTS

During the period from 1990 to 1999 inclusive, 368 cases of head and neck cancer had been registered at the outpatient clinic of Clinical Oncology and Nuclear Medicine Department of Mansoura University Hospital.

Reliable data concerning the clinico-epidemiological and therapeutic features of only 188 cases of squamous cell carcinoma out of 302 was available. Patient and tumor characteristics of the 188 cases are shown in table 1.

The majority of our cases presented in the 6th decade and above. The mean age at diagnosis was 53.5±13.8 years. Males accounted for 88.3% of the patients. Hoarseness and dysphagia were the commonest presenting symptoms (82%). The majority of the cases (66.3%) had performance status III. The larynx was the most frequent primary site involved (55.3%), followed by the nasopharynx (22.3%).

Advanced stages (III and IV) constituted 75.5%; while tumors of 4 cm size or more existed in 55.3% of cases. Grade II was the commonest grade encountered (42.6%). The majority of patients were chronic smokers (88.3%). Moreover all the females were passive smokers. The number of smokers consuming both goza and cigarettes exceeded those consuming either type alone. Ninety-seven percent of all the smokers have been smoking for more than 20 years.

Regularity of the radiotherapy treatment course

Twenty cases (11%) of the present series had experienced unscheduled treatment breaks, in 12 cases it was due to machines' function problems, in 5 cases due to toxicity reactions and in 3 cases due to official holidays. This treatment breaks ranged from 1 to 12 days.

Survival data of the 188 cases

The median event-free survival was 14 month (range: 1 to 143 months). On the other hand, the median overall survival duration was 22 months (range: 5 to 144 months). The 5-year event-free and overall survival of the 188 cases was 45% and 53%, respectively (Figures 1 and 2).

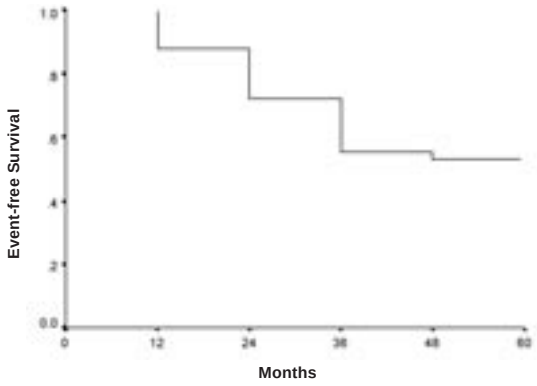

Fig 1. Event-free survival of all cases

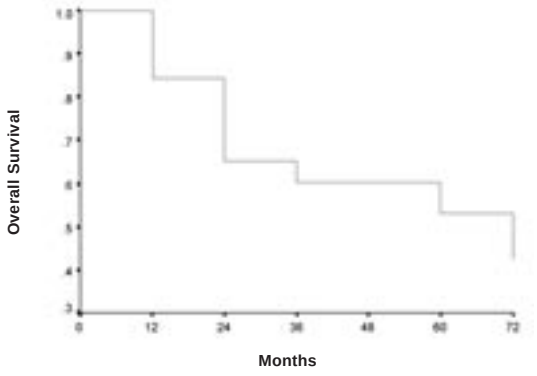

Fig 2. Overall survival of all cases

Table 1
Patient and tumor characteristics

Characteristics	Number	Percent
Age		
< 50 years	81	43%
≥ 50 years	107	57%
Sex		
male	166	88.3%
female	22	11.7%
Presenting symptom		
Hoarseness	51	27%
Dysphagia	31	16%
Nasal obstruction	24	13%
Stridor	18	9.5%
Tinnitus	17	9%
Epistaxis	15	8%
Headache	15	8%
Nerve palsy	8	4%
Mass	7	3.7%
Excessive salivation	3	1.2%
Performance status scale		
0-2	69	36.7%
3	119	63.3%
Site of primary tumor		
Larynx	104	55.3%
Nasopharynx	42	22.3%
Hypopharynx	23	12.2%
Oropharynx	4	2.1%
Oral cavity	11	5.9%
Maxilla	2	1.1%
Unknown	2	1.1%
Size of tumor		
< 4 cm	84	44.7%
≥ 4 cm	104	55.3%
Primary tumor satus		
T0	4	2.1%
T1	34	18.1%
T2	33	17.6%
T3	68	36.2%
T4	49	26.1%
Lymph node status		
N0	116	61.7%
N1	35	18.6%
N2	27	14.4%
N3	10	5.3%
Distant metastasis	6	3.2 %
Stage		
Stage I	30	16%
Stage II	16	8.5%
Stage III	70	37.2%
Stage IV	72	38.3%
Grade		
Grade I	66	35.1
Grade II	80	42.6
Grade III	42	22.3

Prognostic factors affecting event-free and overall survival of 188 cases

On univariate analysis, the significant prognostic factors affecting event-free survival were performance status (p <0.001), for grade I versus grade II (p=0.002) and for grade II versus III (p=0.031) and tumor size (P=0.033). Stage, sex and age were non significant (p=0.13, 0.2 and 0.4, respectively). On multivariate analysis performance status and grade were of statistical significance (p=0.017 and 0.023).

On univariate analysis, the significant prognostic factors affecting overall survival were performance status (p <0.001), size (p=0.005), grade (p=0.004 and 0.041) and stage (p=0.012). Age and sex were non significant (p=0.5, 0.5, respectively). On the other hand, multivariate analysis detected two significant factors that were performance status (p < 0.001) and stage (p=0.0013).

Tables 2-5 present the prognostic factors of both event-free and overall survival.

Table 2
Univariate analysis of prognostic factors affecting event-free survival

Factor	No of patients	Percent	Risk ratio	95% confidence interval	P value
Performance status					
0-2	69	36.7%			
3	119	63.3%	37.61	8.65-30.7	<0.001
Grade					
I	66	35.1%			
II	80	42.6%	4.28	1.47-14.7	0.002
III	42	22.3%	2.08	0.69-7.06	0.031
Size					
<4 cm	48	44.7%			
≥4 cm	104	55.3%	2.31	0.95-5.76	0.033
Stage					
I & II	46	24.5%			
III & IV	142	75.5%	1.80	0.68-4.49	0.13
Age					
< 50	81	43.0%			
≥ 50	107	56.9%	0.03	0.01-0.08	0.40
Sex					
Male	166	88.3%			
Female	23	12.2%	2.05	0.45-19.5	0.27

Table 3
Multivariate analysis of prognostic factors affecting event-free survival

Factor	Risk ratio	95% confidence interval	P value
Performance status	15.61	5.9-13.2	0.017
Grade	3.21	2.9-6.9	0.023

Table 4
Univariate analysis of prognostic factors affecting event-free survival

Factor	No of patients	Percent	Risk ratio	95% confidence interval	P value
Performance status					
0-2	69	36.7%			
3	119	63.6%	15.36	5.65-47.7	<0.001
Size					
<4 cm	84	44.7%			
≥4 cm	104	55.3%	2.80	1.25-6.45	0.005
Grade					
I	66	35.1%			
II	80	42.6%	3.27	1.32-8.47	0.004
III	42	22.3%	2.60	0.95-9.32	0.041
Stage					
I & II	46	24.5%			
III & IV	142	75.5%	2.96	0.96-5.19	0.012
Age					
< 50	81	43%			
≥ 50	107	56.9%	1.52	0.69-3.33	0.35
Sex					
Male	165	87.8%			
Female	23	12.2%	0.84	0.20-2.78	0.51

Table 5
Multivariate analysis of prognostic factors affecting overall survival of 188 cases

Factor	Risk ratio	95% confidence interval	P value
Performance status	12.5	3.5-20.1	<0.001
Grade	2.69	1.7-5.32	0.013

Pattern of failure

Local failure in the present study exceeded in incidence both nodal and distant failure and was diagnosed in 40% of the cases, while nodal and distant failure occurred in 12.6% of cases. None of the cases had more than one type of failure.

Treatment toxicity

The high grades of acute and late toxicities of the present study are shown in tables 6 and 7. Mucositis was the commonest acute toxicity while xerostomia was the commonest late toxicity. Generally higher grade of toxicity were rare.

Laryngeal squamous cell carcinomas

The larynx was the commonest site of primary tumor in this study as the laryngeal squamous cell carcinoma cases constituted 55.3% of the study population. Advanced staged tumors predominated (69%) and were treated by two treatment modalities, surgery followed by radiotherapy in 60 cases and radical radiotherapy in 12 cases.

The difference in the 5-year event-free survival was statistically non-significant (p=0.058) while the difference in the 5-year overall survival was statistically significant (p= 0.036). The 5-year overall survival of all our laryngeal squamous cell carcinoma cases was 60% (Figure 3).

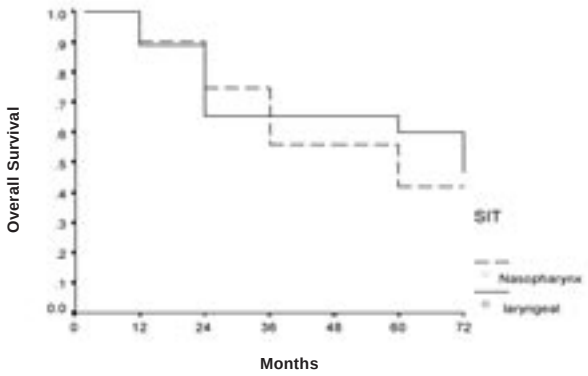

Fig 3. Overall survival of laryngeal and nasopharyngeal cases

Table 6
Grades 3 and 4 acute toxicity of radiotherapy

Toxicity	Number	Percent among 188 cases
Mucositis	11	5.9%
Dermatitis	7	3.7%
Xerostomia	0	0%
Hematotoxicity	0	0%
Dysphagia	0	0%
Total	18	9.6%

Table 7
Grades 3 and 4 late toxicity of radiotherapy

Toxicity	Number	Percent among 188 cases
Mucositis	0	0%
Dermatitis	2	1%
Xerostomia	5	2.6%
Dysphagia	3	1.6%
Osteoradionecrosis	0	0%
Pharyngeal stricture	3	1.6%
L' Hermitte syndrome	0	0%
Total	13	6.9%

Nasopharyngeal squamous cell carcinomas

The nasopharynx was the second most common site of primary tumor constituting 22.3% of the study population.

Similar to laryngeal squamous cell carcinomas, the advanced stages predominated (81%) and were treated by either radical radiotherapy alone (28 cases) or by concomitant chemoradiotherapy (6 cases).

The differences in response rates and the 5-year overall survival of the two treatment modalities were statistically non-significant (p=0.1 and 0.4, respectively). The 5-year overall survival of the nasopharyngeal squamous cell carcinoma cases as a whole was 42% (Figure 3).

DISCUSSION

Head and neck cancer is a term that covers a heterogeneous patient population. It constitutes 6% of all cancers that yearly present to our department, and the squamous cell carcinoma represents the commonest pathological type.

In this study we tried to present the 10-year experience (from 1990 to 1999 inclusive) of our Clinical Oncology and Nuclear Medicine Department in head and neck squamous cell carcinoma. The vast majority of our cases (57%) presented between the 6^{th} and 8^{th} decades of life. This coincides with many of the published literature including that of Hassan et al. (5) who reported that cases above 50 years represented 74% of his cases. Our male to female ratio was 7.5:1 that is larger than several reported literature as that of Gaspar et al. (12) and Busquets et al. (3) who reported ratios of 3:1 and 5:1, respectively. The rarity of smokers among females in our locality might be an explanation.

The most frequent anatomical site of primary tumor was the larynx and this coincides with many literatures as Jones et al. (13).

The majority of the cases presented with pathologic grades 2 and 3 and in advanced stages (3 and 4). This parallels the results of Gaspar et al. (12) who reported 91% incidence of grades I & II and 78.6% incidence of stage IV cases.

Radical radiotherapy alone was the most common treatment modality (57%). Those who received radiation treatment alone due to either inaccessibility or inoperability of the tumors exceeded in number those who received such treatment to preserve organ function in operable tumors. Retrospective studies like that of Busquets et al. (3) reported also that radical radiotherapy was the most common single modality of treatment (96%) however it was applied mainly to preserve organ function in cancer stages amenable to surgery.

The 5-year overall survival of this study (53%) was very similar to many of reported studies like that of Smith et al. (2) and Barzan et al. (14) who published 5-year overall survival figures of 52% and 51%, respectively. It is worth to note that some and not all of the studies that modified their radiation treatment by altering the fractionation or using concomitant chemotherapy like that of Kajanti et al. (15) and Garden et al. (16), had achieved better survival rates. The former reported a 3-year overall survival of 73% while ours was 59% and the latter reported a 5-year overall survival of 64%. Consequently more than one studies are going on in our department now to disclose this issue.

In our study clinical variables that were significant survival predictors in multivariate analysis were performance status, stage and grade. These results cope with the reports of Fang et al. (17) and Nemeth et al. (18) and disclose the important role of early detection of cancer.

Failure at the primary site was the commonest pattern of failure in the present study (40% of the cases). This result goes in harmony with the results of Ma et al. (19) and Luukkaa et al. (20). Their reported incidences of failure at the primary site were 18.4% and 27%, respectively while nodal and distant failures occurred in 1.8% and 12% of the cases, respectively. Such result clarifies the important role of local control in the success of head and neck squamous cell carcinomas treatment.

Our high incidence of failure in general (53% of the cases) might be attributed to under usage of chemotherapy and unscheduled treatment breaks.

Acute radiation toxicity of high grades occurred generally in less than 10% of our cases. This percentage is more

favorable than figures reported in many series that applied chemoradiotherapy to all their cases or altered fractionations of radiotherapy as Corry et al. (21), Forastiere et al. (22), de la Vega et al. (23), Katori et al. (24) and Maguire et al. (25). Their reported high-grade toxicities reached 57%, 82%, 68%, 79% and 100%, respectively.

The most common late toxicity recorded in our study was xerostomia. This result parallels that of Denis et al. (26). We did not report cases suffering from osteoradionecrosis and L'Hermitte syndrome unlike many of the literature that reported these complications after altered fractionations of radiotherapy used concomitantly with chemotherapy as Abitbol et al. (27) and Maguire et al. (25). It is well known that in spite of the fact that altered fractionated radiotherapy and concomitant chemoradiotherapy frequently increase the severity and types of toxicity, they succeeded in many studies in improving the survival figures to values higher than ours while keeping the toxicity within the generally acceptable ranges as the figures reported by Abitbol et al. (27) and Maguire et al. (25). They reported 2-year overall survival figures of 67% and 80%, respectively, while our 2-year overall survival was 63%. With more advancement in the techniques of precise radiation beam delivery it is anticipated that acute and late toxicity rates will show marked decrease in the future decades.

Regarding advanced laryngeal carcinoma cases, a statistically better 5-year overall survival was achieved in the group treated by surgery followed by radiotherapy than that achieved by the group treated by radical radiotherapy alone. There was also a tendency towards better event-free survival (Tables 8 and 9). Such survival benefits were also reported by Patel et al. (6) and Bhalavat et al. (28). In spite of the better survival figures of the group treated by surgery followed by radiotherapy we should not neglect that all such patients lost their voices. In the present years, we are more interested in applying organ preservation treatment in our department. Organ preservation treatment such as induction chemotherapy followed by concurrent chemoradiotherapy is under intense investigation all over the world as reported by Psyrri et al. (29) and Brockstein et al. (30).

The 5-year overall survival of the whole laryngeal squamous cell carcinoma was 60%, a figure similar to that reported by Bien and Zylka (31) and Ge et al. (32) who reported 5-year overall survival figures of 61.7% and 61.8%, respectively.

Considering advanced nasopharyngeal squamous cell carcinoma, Ma et al. (19), Oh et al. (33), Farias et al. (34) and others had reported that such carcinomas are chemosensitive and better treatment results could be achieved with concomitant chemoradiotherapy rather than using either radiotherapy alone or neoadjuvant chemotherapy alone. However, in the present study we failed to detect a beneficial effect of concomitant chemoradiotherapy over radiotherapy alone and this might be attributed to the small number of cases.

The 5-year overall survival of the whole nasopharyngeal group of our study (42%) was slightly inferior to that of Gaspar et al. (12) who reported 45.5%, however it was evidently inferior to many results of other literature as Wolden et al. (35), Ma et al. (19), Chow et al. (36) and Waldron et al. (37) who reported 5-year overall survival figures of 53%, 56%, 62% and 88%, respectively. That inferiority in spite of similarity in the patient population and treatment applied might be attributed to the delayed start of treatment, the unscheduled treatment breaks and under usage of chemotherapy.

CONCLUSION

The majority of our head and neck squamous cell carcinomas were chronic smokers presenting with advanced stages of the disease and suffering from a more or less defective performance status. Both disease stage and performance status were found to have a crucial impact on survival. Consequently controlling risk factors and early cancer detection are urgently required to decrease the incidence and increase survival duration of such tumors. More effort should be paid to avoid unscheduled treatment breaks that affect our survival figures.

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