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Original Article

PATTERNS OF TREATMENT FAILURE, PROGNOSTIC FACTORS AND SURVIVAL IN LOCOREGIONALLY HEAD AND NECK CANCER PATIENTS

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ABSTRACT

Patient Methods: Two hundred and thirty previously untreated patients with head and neck squamous cell carcinoma (HNSCC) were followed up. The following parameters were studied: age, sex, clinical T and N stage, histology grade and anatomic site of the tumor, smoking status and performance. Photon energy, radiation dose, and treatment duration were also recorded. For the postoperative patients, the surgical margin status, number of positive and excised nodes, and tumor size were recorded. Each patient underwent a physical examination, complete blood count, serum chemical profile, chest radiography, dental evaluation, and a full endoscopic examination. Computed tomography of the site of the primary tumor and the neck was done. During treatment, patients were examined at least weekly. Once treatment ended, an evaluation was required at 9 weeks then every two months for the first year, every 6 months for the next two years.

Results: The tumor response, and treatment-related adverse effects were assessed at baseline, and at each follow-up assessment.

The number of HNSCC cases within the period of study was 230 with a relative frequency 10% to all malignancies. The median age of our patients was 54 years with male to female ratio of 5.5 to 1, and according to the Karnofsky performance status 4.4% of patients had KPS of 60%. The number of cases with grade II tumor differentiation was significantly higher than those with grade I or grade III ($p< 0.001$). Patients who had no further disease during follow up were significantly higher among the group with tumor margin free after surgery. Patients who had loco regional recurrence were significantly higher among the group with tumor margin not free after surgery, while no significant difference was found between the to groups regarding distant metastasis. Of the 90 patients who underwent surgery, the surgery of 50 cases had been complete. In 40 patients, tumor excision was incomplete. Analysis of different prognostic factors in this study showed that stage, and hemoglobin level have a significant impact on the disease-free and the overall survival.

Key Words: Chemoradiotherapy, head and neck cancer, patterns failure, prognostic factors, tumor margin.

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INTRODUCTION

Head and neck cancer represents about 17% of all malignant tumors in Egypt[1]. Worldwide, it represents the 6th most prevalent cancer. Regarding prognosis, head and neck cancers are classified into favorable and unfavorable sites, with great varieties in 5 year survival rates. The best chance for the cure of a patient with head and neck cancer is his first radical treatment attempt. This is explained by the fact that recurrent head and neck cancer after surgery and/or radiotherapy are poorly salvaged due to the postoperative and postradiation fibrosis. These recurrent head and neck cancers carry an unfavorable outcome and prognosis[2]. Addition of systemic therapy to the standard radiotherapy has 2 theoretical aims. First, to increase locoregional control and second to decrease systemic dissemination. In this regard, several radiotherapy and chemotherapy combinations have been tried to improve the poor survival of patients with bulky primary tumors or with massive lymphadenpathy.[3]

This study was designed to analyze patterns of failure and prognostic factors for locoregional and distant recurrences, progression-free survival and overall survival using 2 different treatment strategies in patients with head and neck cancer. The relation between the histologically determined status of surgical margins and the cause of treatment failure was studied in a sample of surgically treated head and neck cancer patients. The role concurrent cisplatin and radiotherapy in reducing the probability of locoregional failure and distant metastasis compared to radiotherapy alone was assessed among locally advanced cases not amenable for surgery.

PATIENTS AND METHODS

Two hundred and thirty previously untreated patients with head and neck squamous cell carcinoma (HNSCC) were followed up. All were patients presenting to the South Egypt Cancer Institute during the period from January, 2001 to January, 2003. The following parameters were studied: age, sex, clinical T & N stage, histology grade and anatomic site of the tumor, smoking status and performance. Photon energy, radiation dose, and treatment duration were also recorded. For the postoperative patients, the surgical margin status, number of positive and excised nodes, and tumor size (as the product of the two maximum diameters) were recorded. Each patient underwent physical examination, complete blood count, serum chemical profile, chest radiography, dental evaluation, and a full endoscopic examination. Computed tomography of the site of the primary tumor and the neck was done.

Treatment modalities[4]:

Patients with T1/T2 were treated by surgery or radical radiotherapy. For larger tumors, surgery was the first option, and radiotherapy was used when the morbidity associated with surgery was estimated too high.

Patients who underwent primary surgery with curative intent: They were divided into 2 groups. The first group was formed by those with normal epithelial linings at their surgical margins. The second group consisted of those with dysplasia of any grade at the margin and those with incomplete tumor excision.

Incomplete tumor excision meant presence of invasive tumor at the margin or the distance between individual tumor nests being greater than the distance between the resection margin and the tumor nest closest to this margin.

Patients who received radiotherapy were classified into:

- Postoperative adjuvant radiotherapy,
- Radical radiotherapy,
- Or combined with chemotherapy.

Patients received postoperative radiotherapy consisting of conventionally fractionated doses of 2Gy each in 5 weekly sessions. Maximal and minimal target-volume doses and the maximal dose to the spinal cord were recorded. Treatment was conducted on linear accelerators 0f 6 MV with the use of isocenteric techniques. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of up to 54 Gy in 27 fractions over a period of 5.5 weeks. Regions that were at high risk for malignant dissemination or inadequate resection margins received a 12-Gy boost (total, 66 Gy) in 33 fractions over a period of 6.5 weeks. The dose to the spinal cord was limited to 45Gy.

Patients who received definitive radiotherapy alone were treated with external-beam megavoltage irradiation to a total planned dose of 70 Gy. Chemotherapy consisted of 20mg of cisplatin/m² of body-surface area once weekly during the course of radiotherapy. All received prophylactic antiemetic agents.

Follow up:

During treatment, patients were examined at least weekly. Once treatment ended, an evaluation was required at 9 weeks then every two months for the first year, every 6 months for the next two years. The tumor response, and treatment-related adverse effects were assessed at baseline, and at each follow-up assessment.

Study end-points:

The primary end point was local and regional tumor control; failure was defined as the reappearance of tumor in the original tumor bed or the development of cervical-node metastases after treatment.

Secondary end points were disease-free survival, over-all survival, and adverse effects. Disease-free survival was measured from the time of randomization to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary). Overall survival was measured from the date of randomization to the date of death from any cause.

Treatment-related adverse effects were scored according to the WHO Common Toxicity Criteria. Treatment- related adverse effects[5] were categorized as acute (occurring within 90 days after the start of radiotherapy) or late (continuing or occurring after 90 days).

Statistical methods:

The survival functions were calculated for the two-year disease free and overall survival according to the Kaplan & Meier method[6]. The comparison between the survival curves of the different groups was performed using log-rank statistics[7]. Chi-square test was used to compare the distribution of frequencies among various groups.

RESULTS

The total number of adult cancer cases presented to the South Egypt Cancer Institute during the period of study was 2291 cases. The number of HNSCC cases within this period was 230 with a relative frequency 10% to all malignancies.

Table (1) shows patients clinical characteristics, Karnofsky performance status and primary site of the tumor. The median age of our patients was 54 years with male to female ratio of 5.5 to 1, and according to the Karnofsky performance status 4.4% of patients had KPS of 60%.

Table 1: Patient Characteristics.

Characteristic	No. of patients (total 230)	% (total 100%)
Sex:		
M (F)	188 (42)	81.7 (18.3)
Age:		
<60 (>60)	107 (123)	46.5 (53.5)
Clinical presentation:		
Mass	51	22
Hoarseness of voice	92	40
Dysphagia	80	35
Visual disturbances	7	3
KPS:		
60%	10	4.4
70%	18	7.8
80%	79	34.3
90%	123	53.5
Primary site:		
Oral cavity	48	21.3
Nasopharynx	9	3.9
Oropharynx	59	25.7
Larynx	87	37.4
Hypopharynx	27	11.7

Table (2) shows patient classification regarding T&N staging, tumor differentiation and treatment modality. The number of cases with grade II tumor differentiation was significantly higher than those with grade I or grade III ($p< 0.001$).

Table 2: Patient Classification Regarding T and N Staging, Tumor Differentiation and Treatment Modality.

	No. of patients (total 230)	%
T stage		
T1	23	10
T2	41	18
T3	81	35
T4	85	37
N stage		
N0	112	48.7
N1	44	19.1
N2	38	16.5
N3	36	15.7
Tumor Differentiation		
Grade I	69	30
Grade II	115	50
Grade III	46	20
Treatment Modality		
Surgery	50	22
Surgery + Radiotherapy	40	17
Radiotherapy	60	26
Radiochemotherapy	80	35

Table (3) Follow up results of the surgical group. Patients who had no further disease during follow up were significantly higher among the group with tumor margin free after surgery. Patients who had locoregional recurrence were significantly higher among the group with tumor margin not free after surgery, while no significant difference was found between the to groups regarding distant metastasis.

Table 3: Follow up Results of the Surgical Group.

Follow-up data	Tumor-margin free No. (%)	Tumor-margin not free No. (%)	Significance P<
No further disease	38 (76)	16 (40)	0.01
Locoregional recurrence	5 (10)	14 (35)	0.01
Distant metastases	7 (14)	10 (25)	NS
Total	50 (100)	40 (100)	

Out of the 90 patients who underwent surgery, the surgery of 50 cases had been complete. In 40 patients, tumor excision was incomplete conforming to the definition as given before.

Table (4) shows response to radiotherapy and radiochemotherapy.

Table 4: Response to Radiotherapy and Radiochemotherapy.

Treatment Response	Radiotherapy (60 cases)		Radiochemotherapy (80 cases)		
	No.	%	No.	%	Significance (P<)
Complete response	15	25	40	50	0.001
Partial response	27	45	24	30	NS
Stable disease	6	10	4	5	NS
Progressive disease	12	20	12	15	NS

Tables (5-8) and figures (1-3) show relation of the studied variables to response and prognosis.

Table 5: Relation between Response and T-Stage Among Patients Receiving Radiotherapy.

T-Stage	CR		PR		SD		PD	
	No.	%	No.	%	No.	%	No.	%
T1	6	100						
T2	9	90	1	10				
T3			17	68	2	9.5	6	28.6
T4			9	45	4	17.4	6	26.1
P value	0.008		0.007		0.003		0.05	

CR = Complete response, PR = Partial response, SD stable disease, PD = Progressive disease.

Table 6: Relation between Response and T-Stage among Patients Receiving Radiochemotherapy.

T-Stage	CR		PR		SD		PD	
	No	%	No	%	No	%	No	%
T1								
T2			1	6.25				
T3	22	55	14	38.5	2	5	2	2
T4	18	15	10	43.3	2	5	10	25
P value							0.089	

CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease.

Table 7: Significant Prognostic Factors for Disease Free Survival.

Significant Prognostic factor	Radiotherapy Group No of patients with disease free survival (%)	Chemoradiotherapy Group No of patients with disease free survival (%)
Hemoglobin Level		
Anemic patients	7 (33.3%)	10 (35.7%)
Normal patients	18 (46.2%)	26 (50%)
Significance	P < 0.001	P < 0.001
T-Stage		
T1 – T3	25 (93%)	27 (96.4%)
T4	26 (74.3%)	41 (74.5%)
Significance	P < 0.04	P < 0.03

Table 8: Significant Prognostic Factors for Overall Survival.

Significant Prognostic factor	Radiotherapy Group No. of patients with disease free survival (%)	Chemoradiotherapy Group No. of patients with disease free survival (%)
Hemoglobin Level		
Anemic patients	8 (38%)	10 (35.7%)
Normal patients	18 (46.2%)	26 (50%)
Significance	P < 0.001	P < 0.001
T-Stage		
N0 – N1	33 (94.3%)	27 (96.4%)
N2 – N3	25 (73.5%)	30 (75.5%)
Significance	P < 0.04	P < 0.04

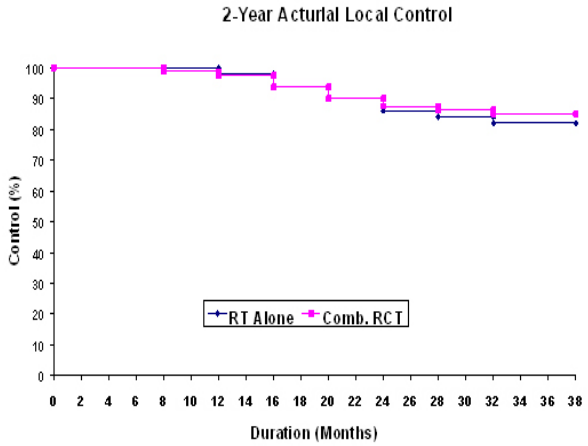

Fig. 1: Two-Year Actuarial Local Control Rate for RT Alone and RCT.

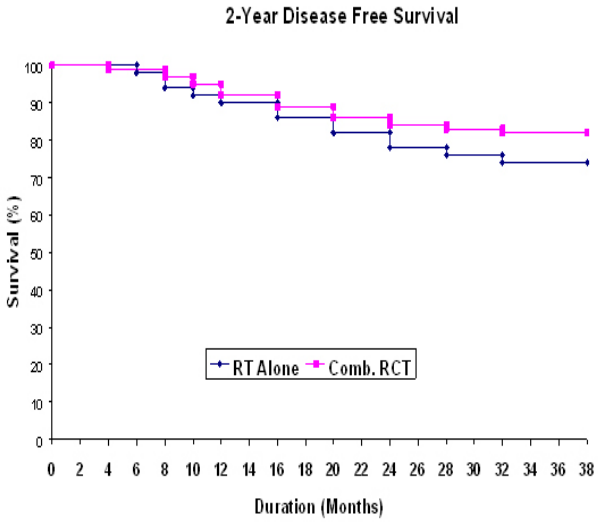

Fig. 2: Two-Year Disease-Free Survival for RT Alone and RCT

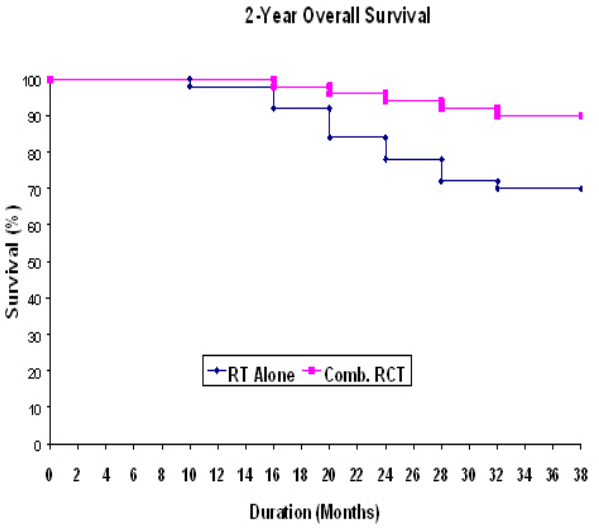

Fig. 3: Two Year Overall Survival for RT Alone and RCT.

No statistically significant relation could be detected between response and age, sex, Karnofsky performance status, pathological grading of the tumor and N-stage of the tumor. Table (9) shows treatment related toxicity in the studied groups of patients.

Table 9: Treatment-Related (grade 3) Toxicity.

Adverse Effect	Radiotherapy (No. of Patients) Total 60	Chemoradiotherapy (No. of Patients) Total 80	Significance
Acute Effects			
Leucopenia	2	8	
Anemia	2	7	
Thrombocytopenia	-	2	
Nausea and Vomiting	-	18	P<0.01
Diarrhea	-	5	
Mucositis	16	20	
Total	20	60	P<0.001
Late Effects			
Dysphagia	6	9	
Xerostomia	2	5	
Hoarseness of Voice	2	2	
Total	10	16	NS

DISCUSSION

It was found that the median age of our patients is 54 years with male to female ratio of 5.5 to 1. This is in agreement with Copper et al.[8] who found that the median age of their patients was 55 years wi6th male to female ratio of 6:1.

The number of cases with grade II tumor differentiation was significantly higher than those with grade I or grade III. This is in agreement with Fortin et al.[9] who found that grade II HNSCC is the most common histological grade.

Most of the patients presented with locally advanced tumor 166 cases representing 72%, 37% of them were T4 and the remaining 35% were T3. T1 and T2 participated by 10% and 18%, respectively. This is in agreement with Lee et al.[10] and Bernier et al.[2] who stated that head and neck cancer commonly presented as locally advanced disease.

Patients who had no further disease were significantly higher among the group who was surgically managed with tumor-margin free than in the group surgically managed with tumor-margin not free. Locoregional recurrence was significantly lower in the tumor-margin free group than in the tumor-margin not free group, while there was no significant difference between the two groups regarding distant metastases (Table 3). This is in agreement with Slootweg et al.[11] who demonstrated comparable results. The occurrence of further disease, locoregional recurrence and distant metastasis in the group surgically managed with tumor-margin free could be explained by the fact that residual cancer cells might remain undetected in the surgical margin by the pathologist [minimal residual cancer][12]. Another explanation was suggested that tumor-related mucosal precursor lesions, "fields" of genetically altered cells, may be left behind, and these might give rise to new invasive carcinomas.[13]

The number of cases who achieved complete response in the group of patients who received combined radiochemotherapy was significantly higher than in the group who received radiotherapy alone (Table 4). This is in agreement with Merlano et al. and Hehr et al.[3,14] who stated that addition of systemic therapy to the standard radiotherapy could improve the poor survival of patients with bulky primary tumors or with massive lymphadenpathy.

T-stage had significantly affected prognosis in patients receiving radiotherapy alone or radiochemotherapy and the disease free survival (Tables 5-7). This is in agreement with Mendenhall et al.[15] who stated that the most important parameter that has an impact on tumor response after treatment is T stage.

For the patients received radiotherapy only and those received the combined radiochemotherapy, the 2-year actuarial estimate of disease-free survival was significantly improved (74% vs. 82%), and so was the overall survival (70% vs. 90%) (Figures 1-3). Merlano et al.[14] found in their trial that the 5 year disease-free survival was 41% and 85%, however the 5-year survival was estimated to be 10% for the patients received RT alone and 24% for those received the combined RCT. The difference between the results of this study and those of their trial may be due to longer period of follow-up with a median of 60 months. Analysis of different prognostic factors in this study (Tables 7-8) showed that stage, and hemoglobin level have a significant impact on the disease-free survival and the over-all survival. This is in agreement with Lee et al.[10]

Acute adverse effects occurred in a significantly higher percentage frequency in the group of patients who received combined therapy than in the group who received radiotherapy alone. The incidence of late adverse effects did not differ significantly between the groups (Table 9). This is in agreement with those results of Cooper et al. which showed similar results.[16]

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