Lead Article

Abstract

36 patients with advanced squamous cell carcinomas of the maxillary sinuses formed the basis of this review. There were 16 T3 and 20 T4. Treatment consisted of radiotherapy alone in 21 cases and radiotherapy followed by systemic chemotherapy in 15 cases. The median survival for all analysed patients was 19 months and the 3-year and 5-year estimated survivals were 30% and 17%. The respective 3- and 5-year survival probabilities were 19% and 9% for patients treated with radiotherapy alone and 40% and 27% for patients treated with radiotherapy and chemotherapy ($p=0.01$). Our findings seem to suggest that the addition of systemic chemotherapy to radiotherapy may improve overall survival in advanced squamous cell carcinomas of the maxillary sinuses.

Squamous Cell Carcinoma of the Maxillary Sinus : A Retrospective Analysis of 36 Cases.

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Cancer of the paranasal sinuses is relatively uncommon, accounting for about 1% of all malignant tumours and about 3% of all head and neck cancers (1). The most frequent site of origin of these tumours is in the maxillary sinuses followed by the ethmoidal sinuses. The common early symptomatology of paranasal sinus cancer is identical to the symptomatology observed in benign conditions, thus the majority of patients present with advanced local disease at diagnosis (2).

The usual methods of treatment of paranasal sinus malignancy consist of surgery, radiotherapy and chemotherapy. Despite all these therapeutic techniques and the advances in surgical approach which now allow extensive tumour resection with minimal cosmetic deformity, the prognosis of patients with advanced disease is still very poor and the optimal therapy remains to be defined (3,4). Local recurrence and stage of the disease are the major prognostic determinants for the overall survival, while the relation of survival to age, histological type, location of the tumour, and treatment modality is not fully defined.

The exact role of chemotherapy in the management of patients with paranasal sinus malignancy is still undefined, mainly because of the small number of studies published and the difficulties in comparing them (4,5). Nevertheless many trials report series of patients with a mixture of different histologic types of tumours, all of which have a unique and in many cases, different biological behavior.

Objective

In order to understand better the efficacy of chemotherapy in the treatment of this tumour we reviewed our experience with patients affected by advanced squamous cell carcinomas of the maxillary sinuses, who had been treated with radiotherapy alone or with radiotherapy followed by chemotherapy.

Materials and Methods

41 patients with histologically confirmed diagnoses of advanced squamous cell carcinomas of the maxillary sinuses were seen at our Institute. Five patients were excluded from the study (2 did not complete therapy, 2 were lost to follow-up within 2 years from the completion of treatment and 1 patient underwent therapy at other institutions). Of the 36 patients analysed, there were 29 men and 7 women (age range 41 to 76 years ; median 65 years) (Table 1).

Table 1

Characteristics of 36 patients with squamous cell carcinomas of the maxillary sinuses treated with radiotherapy (RT) alone or with radiotherapy and chemotherapy (CT)

Treatment	RT	RT + CT
Evaluable patients	21	15
Median age : years	66	65
range	48-76	41-75
Sex		
Male	16	13
Female	5	2
T stage		
III	13	3
IV	8	12

A documented history, a physical examination and and ear, nose and throat examination were performed for all patients. Tomograms were initially used to determine the extent of the tumour. Later, Computed Tomography (CT) and Nuclear Magnetic Resonance (NMR) were used. Common presenting symptoms were facial pain in 67% of patients, nasal obstruction in 36% and facial swelling in 33%. Patients were retrospectively staged according to the American Joint

suprastructure and in 6 they involved the infrastructure only. No patient presented with distant disease.

Tumour unresectability was determined by the surgical members of our multidisciplinary head and neck cancer team at the time of presentation. Potential candidates for surgery were not operated on because of age, poor medical conditions or patient refusal. Criteria for unresectability included ; gross involvement of the brain parenchyma, skull base or orbit-eye ; massive soft tissue disease with or without

Committee for Cancer Staging System (6); the T stage was as follows; 16 T3, 20 T4. Three patients had clinically positive nodes (one had N1 and 2 had N2 neck disease). In 19 of the 36 patients, the tumours involved both the suprastructure and infrastructure, while in 11 the tumours were confined to the

skin involvement ; and encasement of the carotid artery. All patients were adequately followed by more than one otolaryngologist ; patients returned bimonthly for the first 2 years, quarterly during the third year and biannually thereafter on the basis of our follow-up protocol. The local control of the disease was defined

as the complete disappearance of the tumour by clinical examination, tomograms, CT scan and/or NMR for at least 4 weeks after completion of treatment (radiotherapy alone or radiotherapy plus chemotherapy).

Treatment

Treatment varied depending mainly on the existing treatment protocols at the time of diagnosis, the age and medical condition of the patient, and patient preference. Treatment consisted of radiotherapy alone in 21 cases and radiotherapy followed by systemic chemotherapy in 15 cases. Chemotherapy after radiotherapy was given in the attempt to improve the local control of the disease and the overall survival. Because of the lack of effective and widespread chemotherapeutic schedules, chemotherapy began to take part in our treatment protocols in advanced head and neck cancer only from 1979. Therefore all of the eligible patients before 1979 (n=13) were treated with radiotherapy alone. Thereafter chemotherapy was recommended to all patients, but 8 patients received radiotherapy alone (6 refused chemotherapy and 2 did not receive chemotherapeutic drugs because of concomitant diseases).

Radiotherapy was delivered to the primary site by different techniques. The total dose ranged from 3800 to 6800 cGY (median dose 5800 cGY). The neck was included in the radiation field when nodal disease was present.

Systemic chemotherapy was administered 3-6 weeks after the completion of radiotherapy, and varied depending on the existing protocols at the time of treatment. The following chemotherapeutic treatments were used, for a minimum of 2 cycles to a maximum of 6 cycles (median 3 cycles): methotrexate, vincristine and bleomycin (3 cases), cyclophosphamide, vincristine and doxorubicin (3 cases), cisplatin, vincristine and bleomycin (5 cases), 5-fluorouracil and cisplatin (3 cases), cisplatin alone (1 case) (7-9). There was a good balance between patients that received a cisplatin-based regimen and patients who did not receive a cisplatin-based regimen (9 vs 6). No patient had received prior radiotherapy or chemotherapy.

Statistical Methods

Survival was defined as the time from the initiation of treatment to the time of death. Survival distributions were estimated with the method of Kaplan and Meier (10). Survival differences and associations of survival with treatment modality and other patient characteristics (sex, age, location of the tumor, T stage) were analysed by log-rank tests (11). If the associated probability of the best statistic was less than 5% ($p < 0.05$), differences were considered statistically significant. A proportion hazards prognostic factor analysis (multivariate analysis) was performed by Cox regression modeling (12).

Results

Local Control and Recurrence

The overall local control of disease was achieved in 19 of 36 (53%) patients : 11 of 16 T3 stages and 8 of 20 T4 Stages. Local control per treatment modality was 43% for patients treated with radiotherapy alone and 67% for patients treated with radiotherapy and chemotherapy combined ($p = 0.3$).

Sixteen of 19 locally controlled patients had tumour recurrence (84%), either at the primary site (63%), in the neck (5%), or a distant metastasis (16%). Local recurrence occurred between 1 and 38 months after completion of therapy, with an average time of 11 months. Recurrent disease was found in all 3 patients who had positive neck nodes at diagnosis. Sites of distant metastasis included the lung and cervical lymph nodes in 2 patients and the brain in 1 patient. Most treatment failures occurred within 2 years after completion of therapy, the median time of recurrence per treatment modality was 9 months (range 1-13) for radiotherapy alone and 15 months (range 2-38) for radiotherapy and chemotherapy. Many recurrent patients (6/16) received chemotherapy for salvage or palliation; 2 patients received a second course of radiotherapy. The median survival after salvage treatment was 6 months (range 1-18). A surgical approach was attempted in 3 recurrent patients (2 in the radiation group and one in the radiation/chemotherapy group); two of these were alive and disease free.

Survival

Of all 36 patients, 6 were still alive (2 with no evidence of disease and 4 with local recurrence). Four

patients died from causes unrelated to cancer, without local recurrence, between 3 and 9 years after the completion of treatment, while the others died for their disease. The median survival for all analysed patients was 19 months and the 3-year and 5-year estimated survivals were 30% and 17% (Figure 1).

Survival rates were compared according to treatment modality: the respective 3- and 5-year survival probabilities were 19% and 9% for patients treated with radiotherapy alone (median survival, 13 months) and 40% and 17% for patients treated with radiotherapy and chemotherapy (median survival, 27 months) ($p=0.01$) (Figure 2). If the 3 patients who underwent a surgical salvage for their recurrent disease are removed from the analysis the difference in survival probability between the two treatment groups remains statistically significant ($p=0.03$). There was not a statistically significant difference in survival between patients treated with radiotherapy alone before and after 1979 when chemotherapy began to take part in our treatment protocols ($p=0.4$). There was not a statistically significant difference in overall survival between the 9 patients receiving a cisplatin-containing regimen and the 6 patients who did not receive a cisplatin-containing regimen ($p=0.6$).

There was a trend toward longer survival for patients with invasion of the suprastructure (median survival 23 months) with respect to patients with invasion of the infrastructure (median survival, 17 months) ($p=0.08$), and a statistically significant difference in the 3-year probability of survival between patients < 65 years and patients > 65 years ($p=0.02$). There was no significant correlation of survival with the sex of the patient.

There was a statistically significant difference in the survival probability between stages T3 (median survival, 29 months) and T4 (median survival, 10 months) ($p=0.007$) (Figure 3). Multivariate regression analysis revealed that the T4 stage was an independent negative prognostic factor for survival ($p=0.03$). None of the other variables was a good independent predictor of survival.

Discussion

Advanced cancer of the paranasal sinuses is a challenging oncological problem. Because of their proximity to the skull base, central nervous system, and orbit, these tumours cause notable technical

difficulty for both surgeon and radiotherapist. The prognosis remains very poor despite new treatment approaches which are usually designed to achieve the highest possible rate of cure with the least anatomical and functional deformities (3,13).

In this study we reviewed 36 patients with advanced squamous cell carcinomas of the maxillary sinuses seen at our Institute from 1965 to 1992, who were treated with radiotherapy alone or radiotherapy followed by chemotherapy.

The high percentage of local recurrence (63% of 19 locoregionally controlled patients) and the low 3- and 5-year estimated survivals (30% and 17%) confirmed the poor prognosis of advanced squamous cell carcinomas of the maxillary sinuses. Our findings, observed in a population with a substantial proportion of far-advanced disease (T4 lesions), appear similar to those described in other reports in which patients with advanced tumours of the maxillary sinuses were treated with radiotherapy alone, while better results were generally reported with patients treated with a combination of radiotherapy and surgery (2, 3, 13, 14). Nevertheless, clearly progress in surgical technique and the advent of cross sectional imaging together allows surgeons to resect many lesions which would previously been considered unresectable. If this so, it is possible that today many tumours seen in the earlier portion of time span of this work should not be considered truly unresectable and than this could affect in part the data. However, comparison with other series is difficult because of variability in histology, treatment protocols, extent of disease on presentation, and also because literature is limited in this field.

Survival appeared greater in patients treated with radiotherapy and chemotherapy than in patients treated with radiotherapy alone ($p=0.01$) (Figure 2). Although different combination chemotherapies and different radiotherapy techniques were used in a period spanning 30 years, this finding may suggest an important role of chemotherapy as part of a combined treatment of advanced unresectable cancer of the maxillary sinuses. No statistical significant difference was observed between patients treated with radiotherapy alone before and after 1979 when chemotherapy was added in our treatment protocols in patients with advanced cancer of paranasal sinuses. This finding may support the possible benefit of chemotherapy in improving the prognosis of these

patients which does not seem significantly influenced by the development of different radiotherapy techniques in this study. Nevertheless it was not a randomized trial and there may have been some selection bias in this series of cases.

In most trials involving paranasal sinus cancer, surgery and radiation therapy are the mainstays of treatment, while chemotherapy is reserved for patients with far-advanced or recurrent disease. Local control with standard radiation therapy is still suboptimal, with long-term survival less than 10%, and radiation-surgery combinations are also insufficient (2,15). The literature on chemotherapy of carcinoma of the maxillary sinuses is limited because these tumours are rare and many studies are generally reported as part of large trials for head and neck cancer (5, 7, 9). Several reports have described a multimodality treatment consisting of radiotherapy with concomitant intra-arterial chemotherapy and surgery (16). Other studies have reported high response rates in programs using neoadjuvant chemotherapy, although no proven effect on overall survival (17, 18). Nevertheless it seems that the current treatment trends call for preoperative induction chemotherapy rather than postoperative, above all because the dramatic decrease of the tumour would intuitively improve the results of surgery and/or radiation therapy.

In our series, chemotherapy was administered after radiotherapy in an attempt to improve the local control of this disease and overall survival in patients with tumours of the maxillary sinuses which were considered unresectable. The chemotherapy schedules varied depending on the protocols in use at the time, but no statistical significant benefit in overall survival was noted for patients receiving a cisplatin-containing regimen, which is considered the most effective chemotherapy in head and neck cancer (9). The main finding of this retrospective analysis was that treatment with radiotherapy followed by chemotherapy was able to improve survival compared with radiation therapy alone. However, most of the patients treated with radiotherapy alone were older than those in the radiotherapy/chemotherapy group, and age was found to be an important variable in predicting survival ($p=0.02$). Therefore it is possible that the longer survival in the radiotherapy/chemotherapy group was partly a result of the fact that these patients were younger than their radiotherapy counterparts.

Analysis of the other prognostic factors showed that the T stage plays an important role both in the control of disease and in survival. Indeed there was a significantly better survival of T3 than T4 patients ($p=0.007$). This finding is in line with the results of other studies in which the T stage and local control of the disease were the main factors predicting survival in the management of advanced tumours of the maxillary sinuses (3, 13, 14). The number of far-advanced diseases (T4 stage) was higher for the radiation /chemotherapy group than it was for the radiation alone group (12 vs 8), and therefore this could have not led to a falsely improved survival rate for the radiation/chemotherapy group.

Patients affected by tumours located in the suprastructure tended to survive longer than patients with tumours in the infrastructure ($p=0.08$). However patients with infrastructure tumours were generally older than those with invasion of suprastructure and more of them had advanced T4 lesions. Furthermore since only 6 patients had tumours located in the infrastructure, the sample size was too small for reliable conclusions to be drawn. Tumour location has been considered important in other trials and some authors suggest that infrastructure tumours have a worse prognosis than those involving the suprastructure (19). In contrast, other reports indicate a better survival for patients with infrastructure tumours (20).

Conclusion

Although treatment (greater resectability) now differs from the earlier portion of the time span of this work, our findings seem to suggest that chemotherapy administered after radiotherapy should help survival in advanced squamous cell carcinomas of the maxillary sinuses. Our results also suggest that a multimodality approach is needed, especially for the T4 stage which is associated with the worst survival. The advantage of adding chemotherapy to the usual modalities of surgery and/or radiotherapy should be confirmed by randomized controlled trials.

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