Rhinology, 41, 44-48, 2003

Radiotherapy in maxillary sinus carcinomas: evaluation of 79 cases*

Zeynep Özsaran[1], Deniz Yalman[1], Bahar Baltalarlı[2], Yavuz Anacak[1], Mustafa Esassolak[1], Ayfer Haydaroğlu[1]

[1] Ege University Faculty of Medicine Department of Radiation Oncology, Izmir, Turkey
[2] Pamukkale University Faculty of Medicine Department of Radiation Oncology, Denizli, Turkey

SUMMARY

***Purpose**: The aim of this study is to evaluate the outcome of patients with maxillary sinus carcinoma after radiotherapy regarding local control, prognostic factors and morbidity of treatment.*

***Materials and Methods**: Between January 1983 and December 1996, 79 cases of maxillary sinus carcinoma without any evidence of distant metastases, were treated with radiotherapy.*

***Results**: Fifty-two patients (65.8%) were male and 27 (34.2%) were female. The median age was 57. Histologically 62% were epidermoid carcinoma, 32.9% were non-epidermoid carcinoma and 5.1% were unclassified. Sixteen patients (20.5%) had T2, 25 (29.8%) had T3 and 38 (49.7%) had T4 tumour while 13 patients (16.5%) had lymph node metastases. Fifty-nine patients (74.4%) underwent surgical resection followed by postoperative radiotherapy and 20 patients (25.3%) received radiotherapy alone. The median follow-up was 71 months; 5-year overall survival and local control rates were 53% and 54% respectively. Prognostic factors influencing the overall survival were histologic type (epidermoid carcinoma, p=0.02), advanced T stage (p=0.04), postoperative residual tumour (p=0.002) and lymph node involvement (p=0.01) whereas the factors influencing local control were histologic type (p=0.05) and postoperative residual tumour (p=0.005). Late radiation morbidity were cataract (11.4%), loss of vision (8.9%), trismus (5.1%) and hearing loss (2.5%).*

***Conclusion**: In maxillary sinus carcinomas high rates of local control can be achieved with surgery and radiotherapy. Postoperative radiotherapy can have a positive impact on local control and overall survival especially in patients with early stage tumour of non-epidermoid histology and without residual disease after surgery.*

Key words: maxillary sinus carcinoma, radiotherapy, prognostic factors

INTRODUCTION

Paranasal sinus tumours comprise of 0.2-0.5% of all cancer cases and 3% of all cases of head and neck carcinoma and the majority of patients have locally advanced tumours at diagnosis due to nonspecific symptoms. Treatment of these tumours include either surgery, radiotherapy, combined surgery and pre- or postoperative radiotherapy. These modalities have also been combined with local or systemic chemotherapy (Tsuji et al., 1986; Karim et al., 1990; Giri et al., 1992; Sakata et al., 1993; Waldron et al., 2000). Despite the introduction of better imaging (CT and MRI) and surgical techniques it is not possible to remove the tumour with adequate margins even if total excision is performed so adjuvant radiotherapy is mandatory (Tsuji et al., 1986; Karim et al., 1990; Dilhuydy et al. 1993; Stern et al., 1996; Paulino et al., 1998; Le et al., 1999; Jansen et al., 2000; Waldron et al., 2000). Better local control may have a high impact on long term survival for the maxillary sinus carcinomas. Survival rate is between 30% and 60% (Paulino et al., 1998; Le et al., 1999; Jansen et al., 2000; Waldron et al., 2000).

The aim of this study was to evaluate the outcome in patients with maxillary sinus carcinoma following radiotherapy alone or combined with surgery and to assses the prognostic factors influencing local control and survival.

MATERIALS AND METHODS

Patients

Records of 79 patients with maxillary sinus carcinoma who received radiotherapy during January 1983 and December 1996 were evaluated retrospectively.

Fifty-two patients (65.8%) were male and 27 (34.2%) were female. Median age was 57 years (range, 28-88 years). Histologic distribution was as follows: epidermoid carcinoma in 49

* Received for publication: July 15, 2002; accepted: October 10, 2002

Table 1. Patient characteristics.

	No. of patients	%
Age		
Median 57 (range: 28-88 years)		
Gender		
Female	27	34.2
Male	52	65.8
Histology		
Epidermoid carcinoma	49	62.0
Adenoid cystic carcinoma	11	13.9
Adenocarcinoma	6	7.6
Mucoepidermoid carcinoma	3	3.8
Other types	6	7.6
Unclassified	4	5.1
T stage		
T2	16	20.5
T3	25	29.8
T4	38	49.7
Lymph node involvement		
(-)	66	83.6
(+)	13	16.4
Surgical margin status		
Negative	30	50.8
Involved	29	49.2

patients, adenoid cystic carcinoma in 11 patients, adenocarcinoma in 6 patients, mucoepidermoid carcinoma in 3 patients, other types in 6 patients and the histologic type could not be classified in 4 patients. The patients were restaged according to the 1997 AJCC staging system (Le et al., 1999). Sixteen patients (20.5%) had T2, 25 (29.8%) had T3 and 38 (49.7%) had T4 tumour. Nine patients had clinical and 4 patients had pathological lymph node involvement.

Treatment

The treatment was surgery and radiotherapy in 59 (74.7%) patients, and radiotherapy alone in 20 patients (25.3%). Data of 44 patients regarding the type of surgery could be obtained which was total maxillectomy in 28 patients and partial maxillectomy in 16 patients. Of the 59 patients who underwent surgery, 29 (53.7%) patients had positive surgical margins. Radiotherapy was applied with a Cobalt-60 teletherapy machine with a daily fraction dose of 2.0 Gy. The total radiotherapy dose was 50-60 Gy in patients with free surgical margins, 66-70 Gy in involved margins and 66-74 Gy in patients treated with radiotherapy alone. An anterior and a lateral field with wedges was employed to 42 patients and a single anterior field to 37. The target volume included the tumour bed with a 2 cm-margin in operated patients and the tumour volume defined by CT or MRI with a 2 cm-margin in inoperated patients. Regional lymph nodes were not irradiated unless there was an evidence of clinical or pathological involvement. Four patients received concomitant and 5 patients received adjuvant chemotherapy. Patient and treatment charasteristics are indicated in Tables 1 and 2.

Table 2. Treatment characteristics.

	No. of patients	%
Treatment type		
Surgery and radiotherapy	59	74.7
Radiotherapy alone	20	25.3
Type of surgery		
Total maxillectomy	28	35.4
Partial maxillectomy	16	20.3
Status cannot be defined	35	44.3
Total radiotherapy dose		
≤60 Gy	32	40.5
>60 Gy	47	59.5
Total treatment time		
≤50 days	37	48.2
>50 days	42	51.8

Evaluation

The patients were evaluated for the prognostic significance of age, sex, histological type, T stage, nodal involvement, treatment type, total radiation dose, overall treatment duration and surgical margin status on survival and local control. Survival analyses were performed using the Kaplan-Meier method and the log-rank test was used for comparison of the groups. Results were considered to be statistically significant if p was less than 0.05.

RESULTS

The median follow-up was 71 months (range, 3-153 months). Five-year overall survival and locoregional control rates were 53% and 54% respectively. Sixteen patients (25.4%) developed locoregional recurrence; 14 of them were in-field recurrence and 2 were lymphatic recurrence.

Age (≤57 vs >57 years) and gender did not have any prognostic significance for survival and local control. Histologic type (epidermoid vs nonepidermoid histology, p=0.02), T stage (T2 vs T3-4, p=0.04), lymph node status (positive vs negative, p=0.01) and surgical margins (involved vs uninvolved, p=0.002) were significant prognostic parameters for survival. Survival was adversely affected in patients with epidermoid histology, T4 stage, lymph node involvement and involved surgical margins. The type of treatment (surgery and radiotherapy vs radiotherapy alone, p=0.10), total dose (>60 Gy vs ≤60 Gy, p=0.09) and overall treatment duration (≤ 50 days vs >50 days, p=0.20) did not have any impact on survival. Epidermoid carcinoma histology and involved surgical margins adversely affected the local control (p=0.05 and p=0.005 respectively) whereas age (p=0.70), gender (p=0.50), T stage (p=0.30), lymph node involvement (p=0.30), type of treatment (p=0.40), total dose (p=0.40) and overall treatment duration (p=0.50) did not have any impact on the local control.

Thirty-five patients (44.3%) developed early grade I-III mucositis and radiodermitis. Late radiation morbidity were cataract (11.4%), loss of vision (8.9%), trismus (5.1%) and hearing loss (2.5%).

DISCUSSION

The majority of patients with maxillary sinus carcinoma are diagnosed at advanced stages with extensions to contiguous structures including the orbit, nasal cavity, ethmoid sinus, sphenoid sinus, nasopharynx, pterygoid fossa, palate and cheek which can be a therapeutic challenge to both the surgeon and the radiation oncologist (Tsujii et al., 1986; Parsons et al., 1988; Jiang et al., 1991; Giri et al., 1992; Paulino et al., 1998; Waldron et al., 2000). In our study 79.7% of the patients had presented with T3 or T4 tumour and 20.3% with T2 tumour.

Due to the rarity of these tumours most of the reports are retrospective including small numbers of patients and the institutional experience is usually limited. In several studies age, gender, histologic type, stage and type of treatment were reported to be prognostic factors however no multicentric randomized studies are available to evaluate the prognostic significance of these factors (Lee and Ogura, 1981; Parsons et al., 1998; Paulino et al., 1998; Le et al., 1999; Jansen et al., 2000; Waldron et al., 2000).

The influence of the histologic type on local control and survival was evaluated in a study by Le et al. (1999) and no significant difference regarding survival or local control was found among 58 patients with epidermoid carcinoma, 4 with adenocarcinoma, 16 with undifferantiated carcinoma and 19 with adenoid cystic carcinoma. Waldron et al. (2000) stated a similar result regarding the histological type. In the current study epidermoid carcinoma histology adversely affected the local control and the survival (p=0.02 and p=0.05 respectively).

The risk of lymphatic spread is rare because of the poor lymphatic network of this region. Although invasion of the parts with rich lymphatic network such as the oral cavity and nasopharynx increases the risk of lymph node metastases, 3% to 16% of the patients present with lymph node metastases at diagnosis whereas this rate increases from 5% to 48% during the course of treatment (Zaharia et al., 1989; Giri et al., 1992; Parsons et al., 1998; Waldron et al., 2000). Metastasis to cervical lymph nodes generally occurs during progression or recurrence of the primary tumour. Elective irradiation of neck nodes is suggested for patients with nodal involvement (Parsons et al., 1998). Paulino et al. (1997) recommended prophylactic ipsilateral neck irradiation because of their 28.9% neck recurrences in N0 patients and because of the worse overall survival in patients with neck recurrence. Jiang et al. (1991) recommended elective neck irradiation in squamous cell and undifferentiated carcinoma patients due to high nodal recurrence rate in these histologic types. Jansen et al. (2000) found 8 nodal recurrences out of 73 patients and because of this low incidence and the morbidity of neck irradiation they did not favor elective neck irradiation. In the present study bilateral cervical and supraclavicular regions were irradiated only in patients with clinical or pathological lymph node involvement. Waldron et al. (2000) reported a 15% rate of clinical lymph node involvement at the time of diagnosis. It was not associated with a local control, but the survival duration was longer in patients without nodal involvement. In a study by Jansen and associates (2000) lymph node involvement adversely affected local control but had no impact on survival. In the present study nodal involvement was a significant factor for survival but not for the local control (p=0.01 and p=0.30 respectively).

T stage is a strong predictor of survival and local control. In a study by Waldron et al. (2000) the T category was the only factor that significantly predicted local progression-free survival, with T4 tumours having control rates of 31% at 5 years vs. 68% for T2 and T3 tumours; likewise 5-year-survival rates were 68% and 37% for T2-3 and T4 tumours respectively (Waldron JN et al., 2000). In the present study the survival rate was lower in T4 tumours whereas the local control was not affected by T stage (p=0.04, p=0.3 respectively).

Better local control has a high impact on long term survival for the maxillary sinus carcinomas. Surgery and radiotherapy is considered to be the standard treatment modality and the long term survival rate is between 30% to 60% (Parsons et al., 1998; Paulino et al., 1998; Le et al., 1999; Jansen et al., 2000). Table 3 shows the local control and survival rates in different series in patients who underwent surgery and RT versus patients who received RT alone. In the present study although no statistical difference was detected in terms of 5-year survival and local control between the radiotherapy alone group and the surgery

Table 3. Five-year local control and survival in different series by type of treatment.

Series	Type of treatment	No. of patients	5-year local control (%)	5-year survival (%)
Paulino et al., 1998	RT	11	23	0
	S+RT	37	59	52
Lee and Ogura., 1981	RT	35	14	0
	S+RT	61	69	38
Le QT et al., 1999	RT	36	20	19
	S+RT	61	56	46
Current study	RT	20	82 (2 years)	25
	S+RT	59	58	61

RT: Radiotherapy
S+RT: Surgery and radiotherapy

plus radiotherapy group (p=0.10 and p=0.40 respectively), these groups were not comparable due to the difference in number of patients and distribution of T stage in each group. So it should not be interpreted as that comparable results can be obtained with RT alone to that of surgery followed by irradiation.

Local recurrence is the main cause of treatment failure in maxillary sinus carcinoma. The most significant prognostic parameter associated with local recurrence in patients who were treated with surgery and radiotherapy is positive surgical margins. In their study of 149 patients Zaharia et al. (1989) reported a 43% 5-year local control rate in patients with positive surgical margins and 72% in patients with uninvolved margins. Jiang et al. (1991) also reported a 10% reduction in the 5-year local control rate when the margin of resection was involved with disease. In the present study positive surgical margins was an adverse prognostic parameter both for 5-year survival and local control (p=0.002, p=0.005 respectively).

The total radiation dose and overall treatment duration were other significant prognostic factors for local control. Treatment planning and administration of high radiation doses are hampered by tumour location and extension to surrounding structures. If the tumour is removed totally, 60-65 Gy with 1.8-2.0 Gy daily fractions is adequate. In case of macroscopic residual tumour 66-70 Gy should be administered (Tsuji et al., 1986; Parsons et al., 1988; Parsons et al., 1998; Paulino et al., 1998). Giri et al. (1992) reported that a tumour dose >65 Gy resulted in improved local control rates in patients who were treated with radiotherapy alone. Similarly Kondo et al. (1985) reported a 63% 5-year local control rate for patients receiving >60 Gy and 29% for patients receiving ≤ 60 Gy. Le et al. (1999) noted that none of their patients who were treated with a total dose ≤64 Gy achieved local control. In the same study overall treatment duration was a statistically significant independent predictor of local control and it was of borderline significance for survival. The 5-year local control and survival rates were 52% and 49% respectively, for overall time = 50 days and 32% and 18% for overall time ≤50 days (Le QT et al., 1999). In the present study total radiation dose (≤60 Gy vs >60 Gy) and overall treatment duration (≤ 50 days vs >50 days) had no impact on survival or local control but according to our current knowledge unnecessary treatment interruption should be avoided.
The tumours located in this region are surrounded by critical structures such as the base of the skull, cranial nerves, salivary glands, brain, pituitary gland, lens and optic nerves. The aim of radiotherapy should be maximum local control with minimum morbidity. However inclusion of one or more of these organs in the treatment field is inevitable resulting in treatment morbidity. Modern radiotherapy techniques such as 3D conformal radiotherapy and intensity modulated radiotherapy should lead to decreased injury to the surrounding normal tissues. Orbital invasion is one of the problems both for surgery and radiotherapy resulting in ophtalmological morbidity such as loss of vision, conjunctivitis and keratitis when included in the treatment field. Karim et al. (1990) reported a 16% eye damage in 45 patients.

In a study by Jansen et al. (2000) the risk of serious ophthalmological toxicity was 14% when there was no tumour extension through the orbit, whereas toxicity was 33% when there was tumour extension in the orbits. Parsons et al. (1988) reported a 33% incidence of unilateral blindness and an 8% incidence of bilateral blindness in patients treated with curative intent. Jiang et al. (1991) noted a 7% risk of frontal lobe necrosis when a generous superior margin was used to encompass possible intracranial spread. It has also been reported that the most frequent complications were osteoradionecrosis of the antral wall or blindness with the incidence of 20% and 29% at 5 and 10-years of follow-up respectively (Jiang GL et al., 1991). The incidence of late morbidity such as necrosis/fistulas, trismus and osteonecrosis were noted as 3%, 12% and 4% respectively by Paulino et al. (1998). Bedwinek et al. (1976) found that the risk of osteoradionecrosis has increased after 6750 cGy. In the current study our late morbidity rates were as follows: cataract 11.4%, visual impairment 8.9%, trismus 5.1% and hearing loss 2.5%; however the retrospective nature of this study and the lack of pre- and posttreatment data for each patient made it difficult to score the actuarial toxicity.

In maxillary sinus carcinomas a wide variety of therapeutic approaches have been attempted, however the basic problem is local recurrence despite the curative treatment. Due to the rarity of this disease the data from comparative clinical trials is lacking. The majority of the literature supports the superiority of surgical resection combined with radiotherapy than radiotherapy alone (Jiang et al., 1991; Parsons et al., 1998; Paulino et al., 1998; Jansen et al., 2000). The results of the current study showed that postoperative radiotherapy is especially beneficial for patients with early stage, nonepidermoid type lesions, without lymph node metastases and positive surgical margins; however the small number of patients in this analysis and the lack of detailed patient data may precluded any statistical significance of other tumour and treatment related factors.

REFERENCES

1. Bedwinek JM, Shukovsky LJ, Fletcher GH, Daley TD (1976) Osteonecrosis in patient treated with definitive radiotherapy for squamous cell carcinoma of the oral cavity and naso-and oropharynx. Radiology 119: 665-667.
2. Dilhuydy JM, Lagarde P, Allal AS, Becouarn Y, Soubeyran P, Richaud P, Faucher A, Traissac L, Stoll D (1993) Ethmoidal cancer; a retrospective study of 22 cases. Int J Radiat Oncol Biol Phys 25: 113-116.
3. Giri SP, Reddy EK, Gemer LS, Krishan L, Smalley SR, Evans RG (1992) Management of advanced squamous cell carcinomas of the maxillary sinus. Cancer 69: 657-661.
4. Jansen EPM, Keus RB, Hilgers FJM, Haas RL, Tan IB, Bartelink H (2000) Does the combination of radiotherapy and debulking surgery favor survival in paranasal sinus carcinoma? Int J Radiat Oncol Biol Phys 48: 27-35.

5. Jiang GL, Ang KK, Peters LJ, Wendt CD, Oswald MJ, Goepfert H (1991) Maxillary sinus carcinomas: natural history and results of postoperative radiotherapy. Radiother Oncol 21: 193-200.
6. Karim ABMF, Kralendonk JH, Njo KH, Tabak JM, Elsenaar WH, van Balen AT (1990) Ethmoid and upper nasal cavity carcinoma: Treatment results and complications. Radiother Oncol 19: 109-120.
7. Kondo M, Ogawa K, Inuyama Y, Yamashita S, Tominaga S, Shigematsu N, Nishiguchi I, Hashimoto S (1985) Prognostic factors influencing relapse of squamous cell carcinoma of the maxillary sinus. Cancer 55: 190-196.
8. Le QT, Fu KK, Kaplan M, Terris DJ, Fee WE, Goffinet DR (1999) Treatment of maxillary sinus carcinoma. A comparison of the 1997 and 1977 American Joint Committee on Cancer Staging Systems. Cancer 86: 1700-1711.
9. Lee F, Ogura JH (1981) Maxillary sinus carcinoma. Laryngoscope 91: 133-139.
10. Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR (1988) Malignant tumours of the nasal cavity and ethmoid and sphenoid sinuses. Int J Radiat Oncol Biol Phys 1988; 14: 11-22.
11. Parsons JT, Mendenhall WM, Stringer SP (1998) Nasal cavity and paranasal sinuses. Principles and Practice of Radiation Oncology, 2nd edition (Eds: Perez CA, Brady LW). Philadelphia, JB Lippincott, 941-959.
12. Paulino AC, Marks JE, Bricker P, Melian E, Reddy SP, Emami B (1998) Results of treatment of patients with maxillary sinus carcinoma. Cancer 83: 457-465.
13. Sakata K, Aoki Y, Karasawa K, Nakagawa K, Hasezawa K, Muta N, Terahar A, Onogi Y, Sasaki Y, Akanuma A (1993) Analysis of the results of combined therapy for maxillary carcinoma. Cancer 71: 2715-2722.
14. Stern SJ, Hanna E (1996) Cancer of the nasal cavity and paranasal sinuses. In: Myers EN, Suen JY, editors. Cancer of the head and neck. Philadelphia: WB Saunders, 205-233.
15. Tsujii H, Tadashi K, Arimoto T, Mizoe J, Shirato H, Matsuoka Y, Irie G (1986) The role of radiotherapy in the management of maxillary sinus carcinoma. Cancer 57: 2261-2266.
16. Waldron JN, O'Sullivan B, Gullane P, Witterick IJ, Liu FF, Payne D, Warde P Cummings B (2000) Carcinoma of the maxillary antrum: a retrospective analysis of 110 cases. Radiother Oncol 57: 167-173.
17. Zaharia M, Salem LE, Travezan R, Moscol A, Pinillos L, Farias C, Pinillos L (1989) Postoperative radiotherapy in the management of cancer of the maxillary sinus. Int J Radiat Oncol Biol Phys 17: 967-971.

Deniz Yalman
Ege Univ. Tip Fak.
Radyasyon Onkolojisi A. D.
35100 Bornova-Izmir
Turkey

Fax: +90-232-388 4294/117
E-mail: dyalman@med.ege.edu.tr