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Article

**IMPACT OF POST-SURGICAL RESIDUAL TUMOR VOLUME ON LOCAL CONTROL IN RADIOTHERAPY FOR MAXILLARY SINUS CANCER**

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**ABSTRACT**

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**Aim of the Work:** The aim was to study the influence of post-surgical gross residual tumor volume on local control of maxillary sinus cancer treated with radiotherapy combined with debulking surgery.

**Patients and Methods:** 25 patients with squamous cell carcinoma of the maxillary sinus treated by combined surgery and radiotherapy (50–65 Gy, median 60 Gy). Gross residual tumor volume (GRTV) after surgery was measured on computed tomograms obtained after surgery. Patients were classified according to GRTV as follows: group A, GRTV=0 (microscopic residual, n=5); group B, GRTV <10 cm<sup>3</sup> (n=11); group C, 10–40 cm<sup>3</sup> (n=5); and group D, ≥40 cm<sup>3</sup> (n=4). The relationship between local control and GRTV was analyzed using univariate and multivariate analysis.

**Results:** The two years local control rate for all patients was 64%. The differences in local control rates between groups A, B and C were not significant ( $P > 0.05$ ), but the rate was significantly lower in group D than in the other groups (65% at 2 years vs. 25% at one year,  $P < 0.001$ ). Multivariate analysis showed that GRTV ( $P=0.002$ ) and histological differentiation (poorly differentiated histology was favorable,  $P=0.035$ ) were independent prognostic factors and that tumor stage and the sequence of treatment were not.

**Conclusion:** The data suggest that adequate, not complete, debulking associated with the proper dose of radiotherapy can provide satisfactory local control for patients with squamous cell carcinoma of the maxillary sinus.

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**Key Words:** Squamous cell carcinoma of maxillary sinus, radiotherapy, post-surgical residual tumor volume

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**INTRODUCTION**

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Treatment of maxillary sinus cancer is challenging because of the problem of the proximity to critical structures, such as the eye and the brain, which preclude wide surgical excision and high-dose radiotherapy. The clinical course is indolent at most and a substantial proportion of patients have advanced disease at the time of diagnosis. Combined-modality therapy consisting of surgery and radiotherapy (RT) is generally used to treat this disease and the reported 5-years local control and survival rates are 50–78% and 39–64%, respectively. However, an appropriate treatment strategy in terms of surgical procedure, radiotherapy methods and their sequence is still a matter of controversy<sup>1-7</sup>.

In 1970, Sato et al<sup>8</sup> reported that curtailment of the surgical procedures, with the aim of preserving the bony framework of the maxillary antrum, combined with RT and IAC resulted in a significantly better cosmetic and functional outcome as well as an improvement in survival and since then many authors have insisted on the benefits

of piecemeal debulking combined with radiotherapy<sup>5,9,10</sup>. However, conventional two-dimensional RT caused radiation-induced damage of surrounding normal tissues, such as the brain, bone and soft tissue, that was frequently dose-limiting and a total dose of 50–70 Gy per 5–7 weeks of RT was usually adopted<sup>1,2,3,6,8-10</sup>. On the other hand, many authors have reported that whether the tumor volume is less or greater than 30–40cm<sup>3</sup> is crucial to predicting tumor radiocurability of various head and neck cancers with a total dose of 60–70 Gy by conventional or hyperfractionated regimens<sup>11,12</sup>. In this context, how much post-surgical residual tumor volume can be eradicated by a total dose of around 60 Gy per 6 weeks of RT becomes a clinically relevant question. This study was therefore undertaken to analyse the interrelationship between gross residual tumor volume (GRTV) after debulking surgery and local control after RT at a total dose of 50–65Gy per 5–6.5 weeks by the conventional two-dimensional technique.

## MATERIALS AND METHODS

### Patient's Characteristics:

25 patients with biopsy-proven squamous cell carcinoma of the maxillary sinus who presented between June 1997 and September 1999 to the Clinical Oncology and Ear, Nose and Throat Departments, Faculty of Medicine, Zagazig University. All patients underwent surgical excision combined with radiotherapy at a total dose of 50 to 65Gy according to the tumor stage. No patients had distant metastasis at the time of diagnosis.

Disease was classified according to the TNM classification (UICC, 1992) and the stagings of patients are summarized in table 1.

**Table 1:** TNM classification.

	N0	N1	N2	N3	Total
T2	5	-	-	-	5 (25)
T3	5	1	1	-	7 (28)
T4	9	2	1	1	13 (52)
<b>Total</b>	19	3	2	1	25 (25)

### Treatment:

Surgery, consisting of 18 partial and seven total maxillectomies (two with orbital exenteration), was carried out according to the extent of the disease. The transoral approach was mainly adopted and two (15%) of 13 patients with T4 disease underwent total maxillectomy with orbital exenteration. In the remaining patients, the orbital floor was preserved after surgery, even though the tumor had invaded the orbital floor. Eighteen patients underwent postoperative radiotherapy and seven were treated by pre- and postoperative radiotherapy (sandwich treatment) (Table 2).

**Table 2:** Treatment procedures and post-surgical gross residual tumor (GRTV) according to the T classification.

	T2	T3	T4	Total
No. of patients	5	7	13	25
<b>Treatment procedures</b>				
Sx-RT	5	7	6	18
Sx-RT-Sx	-	-	7	7
<b>Residual tumor volume</b>				
Group A (GRTV= 0 cm3)	5	-	-	5
Group B (GRTV <10 cm3)	-	4	7	11
Group C (10-40 cm3)	-	2	3	5
Group D (≥40 cm3)	-	1	3	4
<b>Total</b>	5	7	13	25

Sx, surgery, including piecemeal debulking and total maxillectomy.

Pathological examination revealed a positive resection margin in every case. Five patients who had small disease causing erosion of the hard palate or lateral antral wall (T2) had only microscopic residual tumor. Of the six patients presenting with nodal diseases at the time of diagnosis, five underwent neck dissection and one received definitive RT for nodal disease. No patients without palpable nodes received elective neck irradiation.

RT was carried out mainly with a wedged-pair two-field technique using <sup>60</sup>Co. The total tumor doses ranged from 50 to 65 Gy according to tumor stage (median 60 Gy) and they were given at 2 Gy/fraction, excluding seven patients with T4 disease who received sandwich treatment. Those patients received 30 Gy preoperative RT at 1.5 Gy twice daily and postoperative RT with 40 Gy by conventional fractionation. The median elapsed RT treatment time was 46 days, with a range of 36-90 days and 24 patients (96%) completed their RT within two months. The median duration of treatment as a whole, consisting of surgery and RT, was 55 days, ranging from 46 to 96 days, and in 21 cases (84%) it was completed within two months.

When possible, relapse at the primary site was treated by further surgical excision and isolated nodal recurrence was treated by salvage neck dissection.

CT Volumetry of gross residual tumor volume (GRTV)

Tumor extension into the wall of the maxillary sinus, orbit, pterygopalatine and infratemporal fossa, nasopharynx, ethmoid and sphenoid sinus, frontal sinus and skull base was estimated separately based on preoperative computed tomography (CT) scans and/or magnetic resonance imaging (MRI). Intraoperative findings were also reviewed to confirm the estimates and the residual volume of soft tissue densities, regarded as residual tumors, within each compartment described above was measured on CT scans that were obtained after surgical excision. Therefore, in patients who received sandwich treatment, GRTV means residual tumor volume prior to the postoperative segment of the RT. The residual tumor was outlined and the area was measured with a built-in image analysis system. GRTV was calculated by multiplying each cross-sectional area by slice thickness and adding the slices together. The slice thickness was 5mm in all patients.

### Data Analysis:

Local control was the endpoint of this study. Overall, local relapse-free and disease-specific survival were also analyzed. Survival time was calculated from the commencement of RT. In local recurrence-free survival (LFS), local recurrences and disease-specific death

were counted as failures regardless of all other types of recurrence (nodal and distant). In disease-specific survival (DSS), those who survived after salvage treatment for any types of recurrence were considered successes. These endpoints were estimated according to the Kaplan–Meier method and significance was evaluated by the log-rank test. Multivariate analysis was performed by Cox’s proportional hazards analysis. Data were entered, checked and analyzed using EPI-INFO (version 6.1) software package.

**RESULTS**

**Patient’s characteristics:**

Thirteen (52%) patients had tumors which invaded sphenoid sinus, orbital contents beyond the floor or base of skull (T4) and Six (24%) had neck metastasis at the time of diagnosis. There were 22 men and three women and their median age was 56 years (range: 36–62 years). The length of follow-up was 3–72 months (median: 26 months).

**GRTV:**

In five patients with T2 disease, the gross lesions were completely excised by transoral partial maxillectomy. However, pathological examination of surgical specimens revealed that tumor cells were exposed at the cut edges and GRTV was estimated to be 0cm<sup>3</sup> in all of them (group A). The remaining 20 patients had macroscopic residual disease after excision and the GRTV estimates are shown in table 2. The median GRTV was 7cm<sup>3</sup> and ranged from 5 to 196cm<sup>3</sup>. We patients were classified into group A, B, C or D according to their GRTV as follows: group A, GRTV=0 (microscopic residual); group B, GRTV <10cm<sup>3</sup> (i.e. almost complete resection of the primary tumor); group C, 10cm<sup>3</sup> <GRTV <40cm<sup>3</sup> and group D, GRTV >40 cm<sup>3</sup><sup>9,13</sup>. One the patient in group C had a GRTV of 33 cm<sup>3</sup> (Table 2), the patient remained disease-free for 43 months after treatment by transoral debulking followed by 60 Gy of RT. All of the others in group C had a GRTV of <25cm<sup>3</sup>.

**Local Control:**

Both two and five years local control rates for all patients were 64% (95% confidence interval: 46–78%) and 60% (95% confidence interval: 43–76%), respectively. No statistically significant differences in local control rates were observed between the patients in groups A, B and C, as shown in figure (1, 2). Five patients in group A remained disease-free for 60 months after RT.

Univariate analysis revealed a statistically significant difference in local control rates according to GRTV (group D vs. the others, two year local control rate: 25 vs. 65%, P=0.001) and histopathological grade (poorly vs.

moderately-well differentiated, 2-years local control rate: 100 vs. 47%, P=0.010). T stage (T2/3 vs. T4: 75 vs. 54%, P=0.176) and sequence of surgery and RT (postoperative RT vs. sandwich: 61 vs. 57%, P=0.541) had no influence on local control (Table 3). Multivariate analysis revealed that GRTV (P=0.002) and histopathological grade (P=0.034) were independent prognostic indicators for local control. Among the patients with moderate to well differentiated histology, the influence of GRTV on local control remained significant (57% at 2 years vs. 17% at 6 months, P <0.001).

**Table 3:** Local control rates according to clinicopathological features.

	n	Local Control Rates		p
		2-years % (95% CI)	5-years % (95% CI)	
Overall	25	64 (46-78)	60 (43-76)	
T2	5	100		
T3	7	71 (48-99)	100	
T2/3	12	75 (55-97)	71 (48-99)	T2/3 vs. T4
T4	13	54 (32-76)	75 (55-99)	0.176
<b>Residual tumor volume</b>				
Group A+B	12	67 (48-86)	67 (48-86)	
Group C	5	60 (44-100)	60 (44-100)	
Group A+B+C	17	65 (53-66)	65 (53-66)	A+B and C vs. D
Group D	4	25* (0-67)	-	0.001
<b>Histopathological grade</b>				
Poor**	6	100	100	
mod/well***	19	47 (29-67)	47 (29-67)	0.010
<b>Sequence of surgery and RT</b>				
Postoperative RT	18	61 (46-80)	50 (37-76)	0.541
Sandwich	7	57 (23-97)	-	

CI: confidence interval,

\*: at 1 year

\*\* Poorly differentiated squamous cell carcinoma.

\*\*\* Moderately to well differentiated squamous cell carcinoma.

**Nodal and Distant Failures:**

Six (including three of the six patients presenting with nodal diseases) of 25 patients experienced nodal recurrences as the first events of treatment failure and four were successfully salvaged. Failures at remote sites occurred in the lungs in three patients and in bone in one, and in three they were the first events of treatment failure. The incidence of nodal and distant failure was not correlated with the treatment procedure.

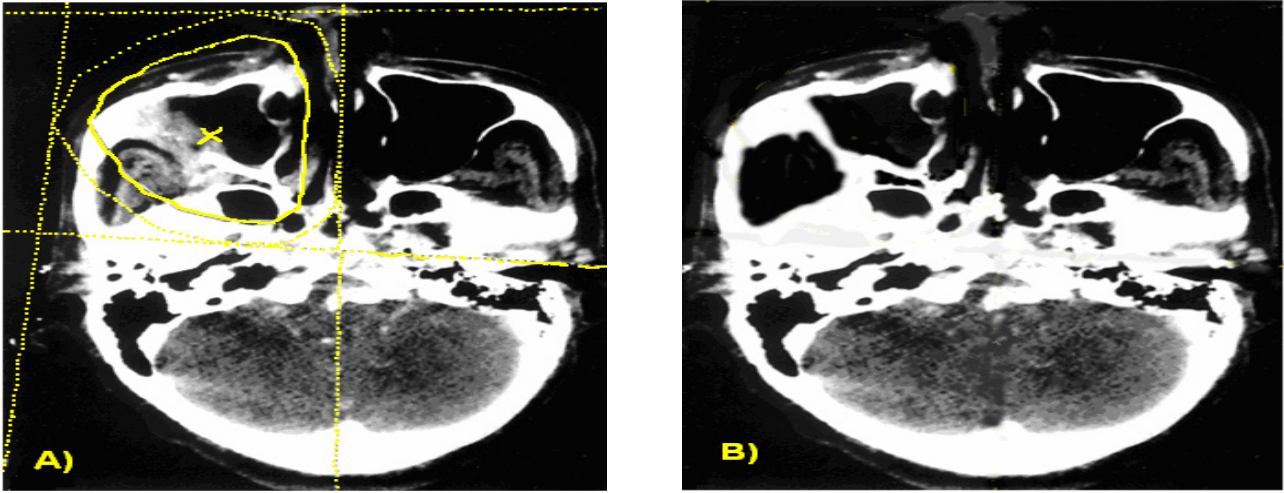


Fig. 1: C.T. images of a patient who had gross residual tumor volume of 35 cm<sup>3</sup> after debulking surgery. (A) Image during radiotherapy planning. This patient was free from recurrence at 3.5 years after radiotherapy (B).

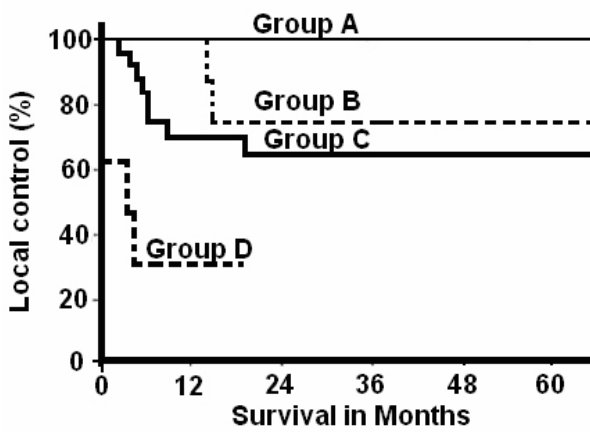


Fig. 2: Local control in patients with squamous cell carcinoma of maxillary sinus according to post-surgical residual tumor volume (GRTV).

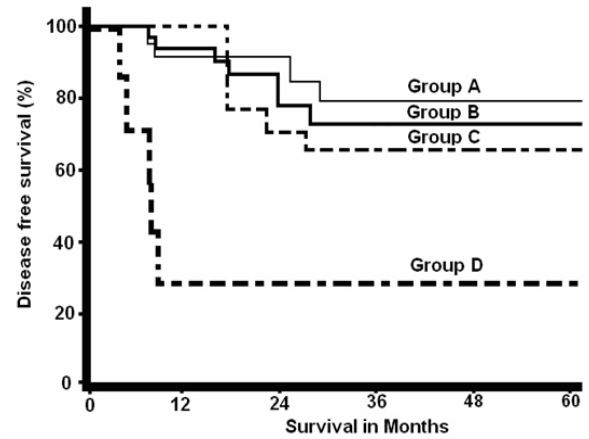


Fig. 3: Disease-specific survival of patients with maxillary sinus cancer classified according to post-surgical gross residual tumor volume (GRTV).

**Survival:**

The cumulative OAS and DSS at two years were 72% (range 57–86%) and 77% (range 63–90%), respectively. DSS at 2 years for the patients in groups A, B and C and in group D were 82% (range 67–97%) and 29% (range 0–63%), respectively ( $P < 0.001$ , Figure 3). All relapses had occurred within 2 years and it was estimated that the two year LFS for the patients in groups A, B and C was 67% (range 50–83%) and that in group D, it was 16% (range 0–44%) ( $P < 0.001$ , Figure 4).

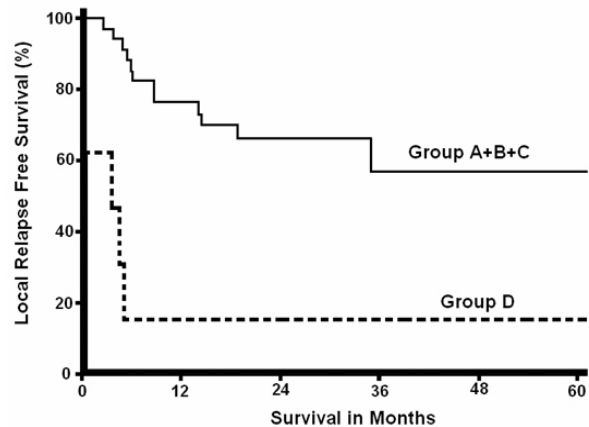


Fig. 4: Local relapse free survival of patients with maxillary sinus cancer classified according to post-surgical gross residual tumor volume (GRTV).



## DISCUSSION

Surgery combined with RT (combined modality therapy) with or without chemotherapy is generally the treatment of choice for maxillary sinus cancer, however, no standard treatment has yet been established<sup>1</sup>. Total maxillectomy with or without orbital exenteration aimed at en bloc excision of the tumor frequently leads to cosmetic deterioration or impairment of eye movement, while transoral piecemeal debulking aimed at preservation of the bony framework of the antrum, frequently leaves gross residual tumor at the excision site. The latter procedure is preferable in terms of cosmetic and functional outcome when the residual tumor can be eradicated by RT<sup>4</sup>. Although many clinicopathological and biological parameters have been reported as indicators of tumor radiocurability, obviously one of the most important prognostic factors is the volume of the tumor<sup>11-14</sup>. In this study, there were significant differences in local control between the patients in groups A, B and C and in group D. Uni- and multivariate analysis showed that GRTV was an independent prognostic factor for local control, whereas T classification (T1-3 vs. T4) was not. These findings suggest that the treatment procedure should not be selected according to the T stage, but on the basis of GRTV according to precise estimations of tumor invasion and the anticipated limits of debulking procedures at the time of diagnosis. Measurement of GRTV on CT images is difficult, mainly because of postoperative inflammatory change. However, adequate estimates can be obtained with regard to tumor extension into adjacent areas according to the preoperative and intraoperative findings. In addition, it is noteworthy that the local control rates of the patients in groups A, B and C were not significantly different, as shown in figure 2. These findings suggest that adequate debulking followed by definitive RT offers the same possibility of local cure as extensive resection.

## CONCLUSION

The results of this study suggest that adequate debulking of squamous cell tumor of the maxillary sinus followed by RT offers a good possibility of local cure even when a certain amount of macroscopic tumor remains unresected. This strategy does not compromise cosmetic and functional results, in contrast to wide resection of the maxillary sinus. Therefore, this procedure could be considered as the treatment of choice for patients whose tumor is adequately debulking even if cosmetically important bony framework of the maxillary sinus, such as orbital floor, is preserved. Aggressive wide resection or further escalation of total RT dose should be considered for those who have more advanced disease.

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