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SURGERY AND POSTOPERATIVE RADIOTHERAPY AND RADIOTHERAPY ALONE IN T3-T4 CANCERS OF THE PYRIFORM SINUS

Treatment results and patterns of failure

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Fifty-four patients with T3-T4 squamous cell carcinomas of the pyriform sinus were treated between 1976 and 1990. Surgery with postoperative radiotherapy (n = 32) was the treatment of choice. Radical radiotherapy was used in patients with contraindications for surgery or with inoperable tumors and in patients who refused surgery. The local control rate was significantly higher in the combined treatment group (31/32; 97%) than in the group treated with radical radiotherapy (14/22; 64%) which consisted of more advanced cases. In patients who received radical radiotherapy, the highest local control rates were recorded with doses of 70 Gy and above and with the use of 2 fractions per day. There was no significant difference in regional control and survival rates between the treatment groups. New approaches are indicated to improve the prognosis of hypopharyngeal cancer.

The hypopharynx is an anatomic area, consisting of the pharyngo-esophageal junction (postcricoid area), the posterior pharyngeal wall and the pyriform sinus. Patients with cancer of the hypopharynx have a poor prognosis. In most cases they present with locally advanced disease or with massive neck disease. Treatment generally consists of surgery and radiotherapy, either alone or in combination. The present retrospective study analyses our experience with surgery plus postoperative radiotherapy and radiotherapy alone in the treatment of patients with locally advanced (T3-T4) squamous cell cancer of the pyriform sinus during a 15-year period.

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Material and Methods

Patients. Between January 1976 and December 1990, 54 patients with T3-T4 squamous cell carcinoma of the pyriform sinus were treated at the Free University Hospital. The median follow-up time was 9 years (minimum 2 years). The general treatment policy for T3-T4 pyriform sinus cancer was laryngo-pharyngectomy with neck dissection followed by radiotherapy. Radical radiotherapy was given in case of contraindications for surgery due to medical reasons, a poor general condition, or in advanced disease considered to be inoperable. Radical radiotherapy was also offered to patients refusing surgery. The mean age of the patients was 64 years (range 43–90 years). Patients were retrospectively restaged according to the 1987 UICC staging system (1). The distribution of tumor stage and nodal involvement at the time of diagnosis is shown in Table 1. The characteristics of the patients treated by surgery plus radiotherapy and radical radiotherapy are shown in Table 2. There were 37 T3 (69%) and 17 T4 (31%) tumors. Forty-two patients (78%) presented with clinically positive neck nodes. There were no significant differences in T- and N-distributions between patients irradiated

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Table 1

T- and N-classification at diagnosis in 54 patients with cancer of the pyriform sinus

	N0	N1	N2a	N2b	N2c	N3	All
T3	8	12	4	8	3	2	37
T4	4	4	1	2	3	3	17
All	12	16	5	10	6	5	54

Table 2

Characteristics of patients treated with surgery plus radiotherapy and with radical radiotherapy

	Surgery plus radiotherapy		Radical radiotherapy	
	n	(%)	n	(%)
All	32		22	
Sex				
Male	26	(81)	19	(86)
Female	6	(19)	3	(14)
Age (mean ± SD)		62 ± 9		66 ± 14
(range)		(44–78)		(43–90)
Differentiation				
Well	1	(3)	3	(14)
Moderately	20	(63)	7	(32)
Poorly	11	(34)	12	(55)
T-classification				
T3	22	(69)	15	(68)
T4	10	(31)	7	(32)
N-classification				
N0	7	(22)	5	(23)
N1	10	(31)	6	(27)
N2	15	(47)	6	(27)
N3	0	(0)	5	(23)

postoperatively or radically. However, all cases with N3 disease were treated by radical radiotherapy. Tumors treated with radical radiotherapy were more frequently poorly differentiated, while those treated by surgery plus radiotherapy were more frequently moderately differentiated.

Treatment. All patients were treated by 4 or 6 MV x-rays using two opposing lateral shrinking fields. Large portals were used for the first 40–46 Gy. The portals were then reduced posteriorly to protect the myelum. The posterior border was then located at the posterior edge of the vertebral body. The dose in the spinal cord never exceeded 50 Gy. After a dose of 50–55 Gy, the field size was further reduced to include only the primary site and the involved lymph nodes. For all fields, individualized cerro blocks were used. The total doses delivered in patients treated with a daily dose of 1.8 Gy were calculated on the basis of a daily dose of 2.0 Gy, using the LQ-model with $\alpha/\beta = 10$ Gy to enable comparison. Radical radiotherapy as primary treatment was used in 22 patients. In 6 cases, 2 fractions per day were given (1.25 Gy/fraction) to a mean total dose of 63.6 Gy (range 61.2–67.5 Gy) and 16 patients received 1 fraction per day (1.8–2.0 Gy/fraction) to a mean total dose of 68.8 Gy (range 57.8–76.0 Gy). In these patients, the total dose did not correlate with grade of differentiation, T- or N-category. In four patients, radical radiotherapy was combined with chemotherapy (cisplatin with or without 5-fluorouracil, or a combination of vincristine, bleomycin and methotrexate). A laryngo-pharyngectomy with unilateral neck dissection was performed in 32 patients. All of them had postoperative radiotherapy (1 fraction/day) to a mean total dose of 61.4 Gy (range 52.4–72.1 Gy). In two patients, a neck dissection was performed, while the primary tumor was not removed. In total, 34 patients underwent neck dissection and in 29/34 cases (85%) there were histologically proven lymph node metastases. In 6 of the 34 patients (18%) the pathological stage was pN1, in 22 patients (65%) pN2 and in one patient (3%) pN3. In 18 of the 29 cases (62%) extranodal tumor growth was observed. Of the 32 tumors removed, 19 (59%) were pathologically staged as pT4. In all patients in whom the tumor was clinically staged as T4 it was confirmed histologically. In 7 cases tumor was shown to be present in the surgical margin, with no significant difference between T3 and T4 tumors. The total radiation dose was significantly higher in the group with tumor at the margin than in those in whom the margins of resection were free of tumor (mean 64.9 Gy and 60.5 Gy respectively).

Statistics. All patients were included in the analysis of survival, local and regional control, and complications. Kaplan-Meier plots for actuarial survival were calculated from the time of completion of radiotherapy and differences between various groups were tested by the log-rank test. The local and regional control rates were also calculated after inclusion of patients who survived at least 1 year following salvage surgery for recurrence (= 'ultimate control').

Results

Local control. A local recurrence occurred in 9/54 cases (17%). In seven of them local failure was seen within the first year after completion of radiotherapy. The local control rate was 31/32 (97%) for surgery plus radiotherapy and 14/22 (64%) for radical radiotherapy. Salvage surgery was successfully performed in one case. In other cases, no salvage surgery was performed due to a poor general condition or the presence of distant metastases. Thus, the ultimate local control rate for radical radiotherapy was 15/22 (68%), which was still significantly lower than in the combined treatment group. Local control was also evaluated in relationship to the total dose delivered (Fig. 1). All (6/6) tumors treated with radical radiotherapy using 2 fractions/day were controlled locally, while in the 1 fraction/day group the local control rate was only 8/16. In patients treated with radical radiotherapy using 1 fraction/day in whom the total dose was less than 70 Gy, the local control rate was 2/8, compared to 6/8 in patients who received 70 Gy or more. There was no significant difference in local control rate between T3 and T4 tumors (Table 3).

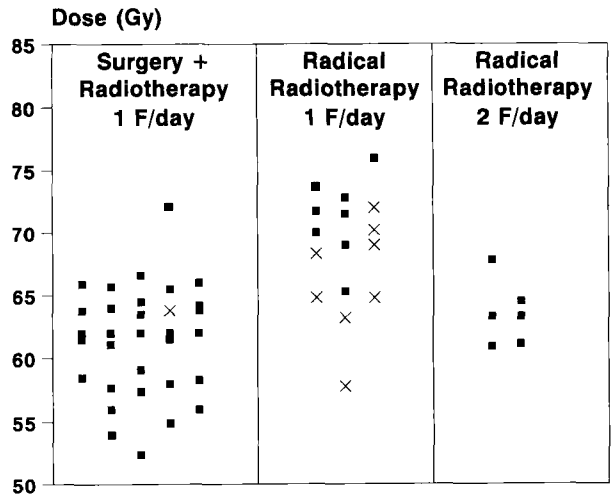

Fig. 1. Local control as a function of total dose (cross indicates failure; box indicates control).

Table 3

Local control in relation to classification

	T3		T4		All	
	n	(%)	n	(%)	n	(%)
Surgery plus radiotherapy	22/22	(100)	9/10	(90)	31/32	(97)
Radical radiotherapy	10/15	(67)	4/7	(57)	14/22	(64)
Surgical salvages/ attempted	0/0		1/1		1/1	
Ultimate control	10/15	(67)	5/7	(72)	15/22	(68)

The local control rate was 24/25 for radically removed tumors and 7/7 for tumors removed irradically (not significant). Nor did the local control rate correlate with lymph node status and histological grade.

Regional control. A regional (neck) recurrence was observed in 12/54 patients (22%); in nine of them, it occurred within the first year after treatment. In the three of the seven patients with regional recurrence following radiotherapy only, salvage surgery was attempted and it was successful in two of them. In the other cases, no salvage surgery was performed due to distant metastases or poor general condition of the patient. The ultimate regional control was 27/32 (84%) for surgery plus radiotherapy and 17/22 (77%) for radical radiotherapy (not significant). The regional control rate related to lymph node status is shown in Table 4. For N0–N2 tumors, the regional control rate was 40/49 (82%), with no significant difference between patients irradiated radically or postoperatively. In patients with N3 disease, the regional control rate was significantly lower (2/5). The regional control rate was 9/11 (82%) for patients without extranodal tumor growth and 14/18 (78%) for those with extranodal tumor growth at histological examination (not significant). Regional control related to the total dose delivered is shown in Fig. 2. In patients treated with surgery plus radiotherapy, there was no correlation between the total dose and the regional control rate. In patients treated with radical radiotherapy using 1 fraction/day who received a total dose less than 70 Gy, the local control rate was 4/8, compared to 6/8 in those where

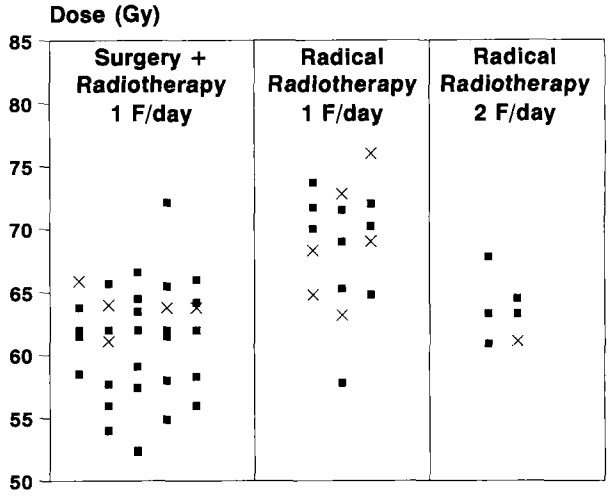

Fig. 2. Regional control as a function of total dose (cross indicates failure; box indicates control).

Table 4

Regional control as a function of N-stage

	N0		N1		N2		N3		All	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Surgery plus radiotherapy	6/7	(86)	8/10	(80)	13/15	(87)	—	—	27/32	(84)
Radical radiotherapy	4/5	(80)	5/6	(83)	4/6	(67)	2/5	(40)	15/22	(68)
Surgical salvages/ attempted	0/0		0/1		2/2		0/0		2/3	
Ultimate control	4/5	(80)	5/6	(83)	6/6	(100)	2/5	(40)	17/22	(77)

the total dose was 70 Gy or more (not significant). In patients treated with radical radiotherapy using 2 fractions/day, there was one regional recurrence. This occurred in patients who received a relative low total dose (see Fig. 2).

Loco-regional control. The combined local and regional control rate was 27/32 (84%) for surgery plus radiotherapy and 11/22 (50%) for radical radiotherapy ($p < 0.01$). The ultimate loco-regional control rate, after salvage surgery for failure after radical radiotherapy, was 13/22 (59%). The two patients who underwent surgery for the neck, while the primary tumor was not removed, both were controlled locally and one of them developed a regional recurrence.

Distant metastases. Nineteen patients (35%) developed distant metastases. In 14 of them (74%) they were detected within the first year after completion of treatment. The most frequent sites of metastases were lung (14), brain (4) and skeleton (4). Three patients had metastases at other sites and 6 patients had metastases in multiple organs. Distant metastases occurred in 12/32 patients (38%) treated with surgery plus radiotherapy and in 7 patients (32%) treated with radical radiotherapy (not significant). There was also no significant correlation between the rate of distant metastases and T- and N-category and histological grade.

Survival. Thirty-one patients (56%) died of the disease and 16 (30%) of intercurrent disease. One patient (2%) is alive with disease and seven patients (13%) are alive with no evidence of disease, after a median follow-up time of 7 years (range 2–13 years). There was no significant difference in survival between the two treatment groups (Fig. 3). Survival at 1, 2 and 5 years was 65%, 41% and 22% respectively. T- and N-category did not correlate with survival. Disease-specific survival was 71% at 1 year, 52%

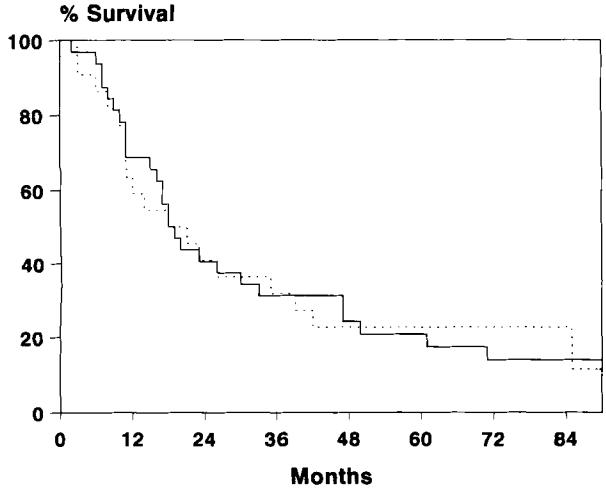

Fig. 3. Actuarial survival for patients treated with surgery plus radiotherapy (——; n = 32) and with radical radiotherapy (· · · · ; n = 22).

Table 5

Cause of death and type of treatment

	Surgery plus radiotherapy		Radical radiotherapy		Total	
	n	(%)	n	(%)	n	(%)
	32		22		54	
Loco-regional	3	(9)	8	(36)	11	(20)
Loco-regional + distant metastasis	2	(6)	3	(14)	5	(9)
Distant metastasis	10	(31)	4	(18)	14	(26)
Total loco-regional	5	(16)	11	(50)	16	(30)
Total distant	12	(38)	7	(32)	19	(35)
Intercurrent disease	12	(38)	4	(18)	16	(30)
Alive	5	(16)	3	(14)	8	(15)

at 2 years and 40% at 5 years, with no significant difference between the treatment modalities. The causes of death for patients irradiated radically and postoperatively are listed in Table 5. The main cause of death of disease was a locoregional recurrence (with or without distant metastases) in patients who received radical radiotherapy and distant metastases (with or without locoregional recurrence) and death of intercurrent disease in patients treated by surgery plus radiotherapy.

Complications. Postoperative complications requiring a second operation were seen in five patients (stenosis of the esophagus (1); pharyngeocutaneous fistulae (4)). One patient developed severe radiation-induced mucositis and was hospitalized for tube feeding. Stenosis of the esophagus occurred in 11/32 patients (34%) treated with surgery plus radiotherapy. Surgery was performed in one patient, whereas the others were treated by dilatation. Myelopathy and other serious sequelae were not seen.

Second primary cancers. Three patients had previously been treated for cancer (oral tongue, larynx and colon). In seven patients one or more second primary cancers were detected after treatment of the pyriform sinus tumor, with a median interval of 6.5 years (range 2–12 years). The sites of the second primaries were: oral/oropharynx (n = 3), bronchus (n = 2), esophagus (n = 2) and prostate (n = 1).

Discussion

The cure rate for squamous cell carcinoma of the hypopharynx is low. This may be explained by the insidious onset and quiescent progression of these tumors. In most cases they are detected in advanced stages with invasion of surrounding tissues. Furthermore, clinically positive neck nodes are found in about 60 to 80% of the cases (2–9). In the present series, 78% of the patients had clinically positive neck nodes on initial presentation. In addition to a general poor nutritional status due to dysphagia, patients with hypopharyngeal cancer frequently also have medical problems associated with alcohol and tobacco abuse, lead-

ing to a high death frequency from intercurrent disease and a high incidence of second primary tumors.

Locoregional recurrence is a major problem in patients with cancer of the hypopharynx. Overall, locoregional control was achieved in 70% of the patients. After salvage surgery for failure after radical radiotherapy, the ultimate locoregional control rate was 74%.

Local control was achieved in about 85% of cases. Others have reported local control rates of about 50 to 65% for radical radiotherapy and 70 to 85% for combined treatment (3, 6, 7, 9–11). Local failure occurred significantly more often in patients treated with radical radiotherapy as compared to those who received the combined therapy which is not astonishing since the radical radiotherapy group included a higher proportion of more advanced cases. The present study suggests that the local control rate of radical radiotherapy can be improved by increasing the total dose (> 70 Gy). The use of multiple fractions per day also appears to result in improved local control. The rationale for using multiple fractions per day is well documented (12, 13).

In patients who receive combined treatment, there was no significant difference in local control rate between patients with radically and with irradically removed tumors. This may be explained by the significantly higher dose used in case of irradicality and the short survival time (median 6 months) due to early distant dissemination in patients with irradically removed tumors.

Radical radiotherapy and surgery plus radiotherapy yielded a regional control rate of 78% with no significant difference between the treatment groups. This concurs with the result from other studies, reporting regional control rates of about 70 to 80% for both regimens (3, 7, 9–11). In patients with N3 disease, the regional control rate was significantly lower than those in other cases. There was no significant difference in regional control between N0, N1 and N2 cases. The presence of extranodal tumor growth was not associated with an increased regional failure rate. This is probably due to the higher (although not statistically significant) dose used in case of node-positive cases and in case of extranodal tumor growth. Similar findings were reported by Leemans et al. (14). These observations show that radiotherapy is effective in controlling neck disease from pyriform sinus cancer. With increasing tumor volume (N3; mass > 6 cm), however, the chances of achieving regional control are significantly lower.

The higher local control rate in patients treated with surgery plus radiotherapy, compared to those treated with radical radiotherapy did not result in improved survival rate or improved disease-specific survival. The high incidence of death from distant metastases and from intercurrent disease contribute to this.

The highest local control rate was achieved in the combined treatment group. Some investigators have advocated preoperative radiotherapy (15, 16), whereas others prefer postoperative radiotherapy (9, 17–19). Although preoperative radiotherapy might have the theoretical advantage of a better oxygen supply to the tissues, it also has disadvantages, since it may make complete resection more difficult and may be associated with an increased frequency of complications (5, 19, 20).

Since this is a retrospective study, where patient selection may have biased the results, no comparisons between surgery plus radiotherapy and radical radiotherapy can be made. The combination of surgery plus postoperative radiotherapy resulted in the highest local control rate. The regional control and survival rates, however, were similiar for radical radiotherapy and surgery plus radiotherapy. Therefore, in patients with contraindications for surgery or with inoperable tumors and in patients who refuse surgery, radical radiotherapy should be used. In order to achieve acceptable local control rates, a high dose (above 70 Gy) should be given. Another option for improvement of local control might be the use of debulking surgery prior to definitive radiotherapy. The poor regional control rate in patients with advanced neck disease might be improved by a limited neck dissection to remove only the main tumor bulk, while sparing non-involved structures, and leaving the primary tumor in situ for radical radiotherapy (21). The high percentage of distant metastases which occur early after treatment, suggest that systemic treatment might be of great value in advanced tumors of the pyriform sinus.

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