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SUPRAGLOTTIC LARYNX CANCER, T1–4 NO, TREATED BY RADICAL RADIATION THERAPY

Problem of neck relapse

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Abstract

The records of 203 patients with T1-4 N0 epidermoid carcinoma of the supraglottic larynx treated at the Dr. Danbiel den Hoed Cancer Center/Rotterdam Radiotherapeutic Institute (RRTI), in 1965–1979 were reviewed. This report is confined to the 165 patients treated by radiation therapy (RT) only and focuses on the problem of relapse in the neck. A comparison is made between patients treated for the primary tumor with RT portals $\leq 30\ cm^2$ and patients treated with larger field sizes. Sixty patients suffered a local recurrence, which was followed by a relapse in the neck in 13 patients. Nineteen patients experienced a relapse in the neck without a previous local failure. Five of these patients experienced a local failure at a later time. A multivariate analysis showed that the risk of a regional failure was significantly higher after a local failure and also for patients treated with small radiation portals ($\leq 30\ cm^2$). Patients with an advanced tumor stage did not have a higher risk of a regional failure. A recurrence in the neck carried a poor survival; nearly two thirds of these patients died of their disease. As a recurrence in the neck seems to be correlated to the control of the primary tumor as well as to the (elective) treatment of the neck, best strategies to further increase the local/regional control are discussed.

Key words: Larynx, neoplasms; supraglottic cancer, clinically negative neck, radiotherapy, neck relapse.

In the treatment of supraglottic larynx cancer, the primary tumor can be controlled by either surgery or radiation therapy (RT). Control of the primary tumor in early stages by either modality appears to be excellent today in competent hands (3, 9, 13, 22, 26, 33, 38). For the more advanced stages, however, most authors favor surgery with or without radiation therapy as the treatment of choice (6, 8, 10, 11, 14, 17, 24, 31). The supraglottic region is abundantly supplied by lymphatics and cervical nodal metastases are a frequent cause of relapse and death of cancer. For the clinically negative neck, debate has often focused on prophylactic treatment of the neck, either by elective neck dissection or by radiation therapy. To study the problem of relapse in the neck we have reviewed the records of all patients with supraglottic larynx cancer with a clinically negative neck, treated for their primary tumor in our institution between 1965 and 1979 with radiotherapy only. We have analysed the data of these patients with two main questions in mind:

1) What was the size of the problem of neck relapse in this patient population?

2) Can prognostic factors for the risk of regional relapse be identified? We will discriminate between factors describing characteristics of the primary tumor (T stage, location and differentiation grade), a factor describing the radiation treatment (field size) and a factor indicating whether or not local control of the tumor was achieved.

Material and Methods

Between 1965 and 1979, 203 patients were treated at the Rotterdam Radiotherapeutic Institute for squamous cell carcinoma of the supraglottic larynx without detectable lymph node and/or distant metastasis (T1–4, N0, M0). Staging was done according to the official classification rules of the UICC (36). All patients eligible for this study were treated by RT only, i.e. patients treated by a combination of radiation therapy and surgery (n=28) or by surgery alone (n=5) were excluded from the present anal-

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ysis. Moreover, 5 patients treated only by RT were not included because of inadequate treatment (total dose less than 40 Gy/early death). The remaining 165 patients, of which 147 (89%) were males, and 18 (11%) were females, form the basis of this report. All patients were irradiated with a once-a-day fractionation scheme (2 Gy per fraction midplane, 5 times per week) by 2 lateral opposed fields on a linear accelerator by a 4 MV photon beam. During the actual treatment the head was fixed in a supine position on the treatment couch with a custom made plastic cast. After a total dose of 40 Gy the response of all tumors was evaluated by the radiation oncologist in conjunction with an ENT surgeon. In general all patients with a good response of their tumors (primary radiation group, RT-I, n=132) continued to a full dose of RT (60–70 Gy). For small, i.e. T1/T2, tumors (n=96) the protocol allowed for either a continuous or a split course technique; in about half of the cases (45%) a continuous course was preferred. For the more advanced tumors (n=69), however, a continuous course technique was used in the minority of the patients (19%).

Patients with a poor response of their primary to RT were submitted for surgery, i.e. partial or total laryngectomy (not included in this study). However, in case of patient refusal and/or if medically unfit for operation, these patients were offered a second course of RT (secondary RT group, RT-II, n=33). The patients of the RT-II group were also subject of the present analysis. Almost all of these patients (32 out of 33) presented with T3/T4 tumors. Moreover, in the majority (73%) of cases the RT was given by a split course technique. A summary of the patient characteristics of the RT-I and RT-II groups regarding tumor stage and treatment of the primary tumor can be depicted from Table 1. Over the years of this particular study period the treatment philosophy has been adhered to rather consistently. However, in 1975 a protocol change was made, specifically regarding the treatment of small supraglottic cancers. Before 1975 a significant number of T1/T2 tumors were treated by small portals, i.e. a field size smaller than 5×6 cm^2. In order to treat the neck electively, as from 1975 larger portals were used for all tumor stages, thereby radiating the upper, middle and lower jugular chain nodes to a dose of 40 Gy. Subsequently a cone-down of the target volume was performed to limit the RT to the primary tumor site only. The relation of field size and tumor stage for the different time periods is shown in Table 2.

Statistical methods. Part of the analysis is devoted to the relation between characteristics of the radiation treatment and the risk of regional failure. One factor has been chosen for this purpose i.e. the field size. When radiation was given in 2 series, the field size was defined as the maximum of the 2 field sizes. A field size less than 30 cm^2 implies the absence of irradiation of the neck (RN−); larger field sizes will be considered as at least partly elective irradiation of the neck (RN+). However, field size may only be considered as a proxy for whether or not elective irradiation of the neck was given in the sense that all the lymph nodes were included in the field. Anatomical properties of the patient and the shape of the field should also be taken into account, but this could not be done in a quantifiable way on the basis of data from the charts. In the analysis we will therefore use only field size and will determine if larger fields are associated with less regional relapses.

The proportional hazard model of Cox (7) has been used to estimate the strength of the association of field size and neck dose with the risk of regional failure. In this multivariate model also other factors are taken into account, i.e. the location of the primary tumor (subregions), T stage, differentiation grade and local control of the tumor as a time dependent covariate.

Table 1

Patients with different tumor stages (T categories) treated by continuous or split course radiation therapy. RT-I: full course of RT as first choice of treatment modality. RT-II: full course of RT in patients who refused and/or were medically unfit for operation

	RT-I		RT-II	
	Continuous	Split course	Continuous	Split course
1A	9	10	0	0
1B	23	23	0	0
2	10	20	1	0
3	4	12	0	4
4	1	20	8	20

Table 2

Patients with early (T1–2, N0) and locally advanced (T3–T4, NO) epidermoid carcinoma of the supraglottic larynx treated between 1965–1975 and 1975–1979. Some were treated with small portals (≤30 cm^2, RN(−)), the majority with large portals (>30 cm^2, RN(+))

	1965–1975		1975–1979	
	RN−	RN+	RN−	RN+
T1/2	20	34	0	42
T3/4	6	35	0	28

Results

Relapse in the neck. This section contains 2 parts. In the first part the numbers and types of failures are described for subgroups of patients without taking into consideration variations in length of follow-up and period at risk between patients. In the second part the results of a formal statistical analysis with the proportional hazards model, in which length of follow-up and period at risk is taken into account in a proper way, are presented.

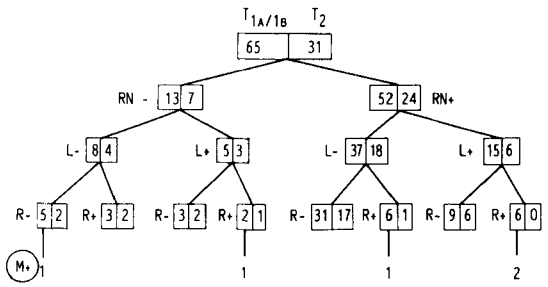

Fig. 1. Patients treated by radiation therapy for stages T1A/1B and T2 cancer of the supraglottic larynx. RN(+)/(−): radiation portal larger than/smaller than or equal to 30 cm^2. L(+)/(−): presence or absence of local relapse. R(+)/(−): presence or absence of regional relapse. M(+): distant metastases.

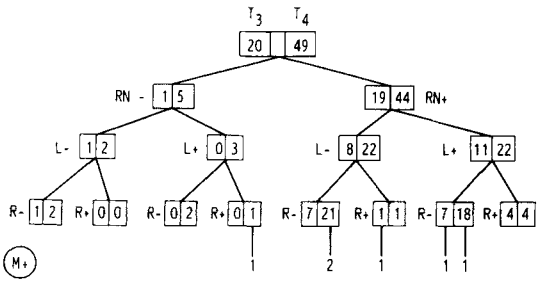

Fig. 2. Patients treated by radiation therapy for stages T3/T4 cancer of the supraglottic larynx. RN(+)/(−): radiation portal larger than/smaller than or equal to 30 cm^2. L(+)/(−): presence or absence of local relapse. R(+)/(−): presence or absence of regional relapse. M(+): distant metastases.

Table 3

Local and/or regional failures and death of all patients with epidermoid carcinoma of the supraglottic larynx (T1–4, N0) treated between 1965 and 1979. NED: No evidence of disease local-regionally in follow-up period

Loco-regional failure	No. of patients			
	Inter-current deaths	Tumor related deaths	Alive	Total
NED	41	5	40	86
Local only	15	17	15	47
Local → regional	0	10	3	13
Regional	5	10	4	19
All patients	61	42	62	165

Figs 1 and 2 show the local, regional and distant failures of the 165 patients with T1–4, N0 supraglottic cancer in relation to tumor stage as well as to whether the neck was irradiated electively or not.

A summary is presented in Table 3, last column. A local or regional failure was observed in 79 patients. Forty-seven patients presented in time with a local failure only, and 13 patients experienced a local failure eventually followed by a regional relapse. Nineteen patients had a regional failure and 5 of these experienced a local relapse at a later time. Thus, of the 165 patients a total of 32 (19%) had a relapse in the neck. Most of these relapses (n=28) occurred within 5 years. The actuarial 5-year risk of regional relapse was 20%.

Relapse related to treatment of the neck. Of the 26 patients who had radiation therapy to the primary tumor only (RN−), 9 had a relapse in the neck (35%); 2 of these had an earlier local failure. Of the 139 patients electively irradiated to the neck (RN+), 23 (17%) relapsed in the neck; 14 of those experienced a local recurrence as well. The proportion of neck relapses was smallest for patients treated with fields larger than 50 cm^2 (13/94=14%). For patients with field sizes between 30 and 50 cm^2 it was 22%=10/45.

Relapse related to tumor stage. Of the 96 patients with early stage tumors (T1/T2), 26 (27%) experienced a local relapse. Twenty-one patients (22%) had a regional relapse and 6 of those had failed at the primary tumor site previously. Among the 69 patients with advanced stage tumors (T3/T4) a higher proportion of local relapses was observed, i.e. 49% (34/69). However, a lower number of regional failures was seen; 11 (16%) patients failed regionally, 7 of which after a local failure. The fact that advanced stage tumors generally were treated with larger fields (Table 2) may have contributed to this result.

Relapse related to control of the primary tumor. Sixty patients recurred locally without a previous regional relapse. It can be postulated that these patients might have an increased risk of a regional relapse. However, the crude proportion of neck failures among the patients with a previous local relapse (21%=13/60) and among those still locally controlled (18%=19/105), were not very much different. One should realize, however, that the total period at risk after a local failure is much shorter than the total period at risk of all patients locally controlled. This is due to the fact that the death rate after a local failure is higher. In the multivariate regression analysis we therefore have taken into account the period at risk and also estimated the effect of local failure at the risk of regional failure.

Regional relapse related to subregions of the primary tumor. For 8 different subregions of the supraglottic larynx we have scored for each patient whether or not there was tumor involvement: the suprahyoid epiglottis (percentage of patients with involvement of this subregion: 51%), the arythenoid (33%), the aryepiglottic fold (51%), the junction (22%), the infrahyoid epiglottis (94%), the false cords (70%), the ventricle (46%) and the vocal cords (43%). Only with respect to the aryepiglottic fold there was an indication of a difference in risk of neck failures between patients with involvement (24% of those experienced a regional relapse) and patients without involve-

ment (15% had a neck relapse). Thirty-two patients experienced a relapse in the neck; for 20 patients the relapse was located in the right side of the neck, for 11 patients in the left side and only one patient developed positive nodes in both sides of the neck. No association was found between the side of the regional relapse and the lateralization of the primary tumor; this may be explained by the fact that most of the primary lesions of the 32 patients with a regional relapse were considered midline lesions (n=22). Moreover, in retrospect, the same holds for the relapse rate to the side of the neck related to the site of the bulk of the tumor mass: again no association was found.

Multivariate analysis. Cox regression model was applied to estimate the association between risk of regional relapse and variables describing the location of the primary tumor (the subregions), the T stage, the grade of differentiation, the field size and one time dependent covariate describing whether or not there had been a local failure when at risk for a regional relapse.

Table 4 shows the results of the analysis. Of all subregions only the aryepiglottic fold showed a significant positive association with risk of regional relapse. The field size showed a significant negative trend: smaller fields had a higher relapse rate. Patients with no irradiation of the neck (field size ≤ 30 cm^2, RN−) had a relapse rate 3.4 times as high as the rate for patients treated with fields larger than 50 cm^2. Patients with a field size between 30 and 50 cm^2 showed a slightly higher relapse rate than those treated with larger fields.

A previous local failure was strongly associated with a higher risk of regional relapse. After a local failure the risk of a regional relapse was 3.3 times as high as when there was still local control.

Not included in the model were grade of differentiation (p=0.55) and T stage. T stage was not included although it showed a significant association (p=0.05) with the rate of regional relapse. However, this association was negative, i.e. after correction for the other factors in the model it seemed to be that the advanced stage tumors (T3/T4) had a lower rate of regional relapse than the early stage tumors. However, we believe this to be an artefact of the multivariate analysis. It may be due to the fact that advanced stage tumors had generally been treated with larger fields (Table 2), and also showed a higher local failure rate. In a univariate analysis T was not related to the regional relapse rate.

Salvage and survival. Survival by stage is shown in Fig. 3. The majority of the deceased patients, however, have died due to other causes than larynx carcinoma (Table 3). For 38 patients this other cause was a second primary cancer; most of these second primaries originated in the lung (n=22). The cause of death of 5 patients was unknown; they have been counted as dead due to larynx carcinoma. This explains that 5 patients without a local-regional failure are listed as dead due to larynx carcinoma. One of these 5 died due to distant metastases. Fig. 4 shows the corrected survival by stage, in which only death due to larynx carcinoma counts as failure.

Table 4

Risk of regional relapse, multivariate Cox regression analysis

Variable	β	SE	Relative hazard rate[a]	Likelihood ratio test
Aryepi	0.78	0.39	2.2	P=0.04
Field 30	1.23	0.45	3.4	P=0.03
Field 3050	0.42	0.43	1.5	
Locfail	1.18	0.39	3.3	P=0.003

[a] The relative hazard rate in comparison with the baseline category with value 0. Coding of variables: Aryepi=1 if involved, 0 if not involved; Field 30=1 if ≤ 30 cm^2, 0 if >30 cm^2; Field 3050=1 if between 30 and 50 cm^2, 0 if not; Locfail=1 if local failure before regional relapse, 0 if not.

Table 3 also shows that the majority of the patients with a regional relapse have died due to their larynx carcinoma. Patients with a local failure only had a better prospect: about one third of these patients have died due to larynx carcinoma. A salvage procedure after a local regional relapse was performed in 72 cases by either radiation and/or chemotherapy (n=40) or surgery (n=32). If we regard patients still alive or those who have died from intercurrent disease as successfully salvaged, then 42 patients have been salvaged; 29 by surgery and 13 by radiation and/or chemotherapy.

Discussion

It is now well known that death from intercurrent disease has a major impact on the survival of patients with cancer of the supraglottic larynx (18, 23, 37) and the present analysis confirms these data. According to the overall survival curves (Fig. 3) there seems to have been a constant force of mortality due to all causes during the years of follow-up, resulting in a death rate between 35 and 65 percent at 10 years for the different stages. The survival data corrected for intercurrent death (Fig. 4) demonstrate that the mortality specifically due to larynx cancer was considerably lower for all tumor stages. The 10-year corrected death rate in the early (T1/T2) stages was about 20 percent and in the advanced (T3/T4) tumor stages about 45 percent. The mortality of both groups, however, was still substantial and seems to have been somewhat more concentrated in the first 5 years after diagnosis. Eleven patients died with distant metastatic disease; however, at their time of death all except one had a local and/or regional relapse as well (Figs 1, 2). Therefore, the main cause of death due to cancer of the larynx was a lack of local-regional tumor control.

The treatment options for local control have classically

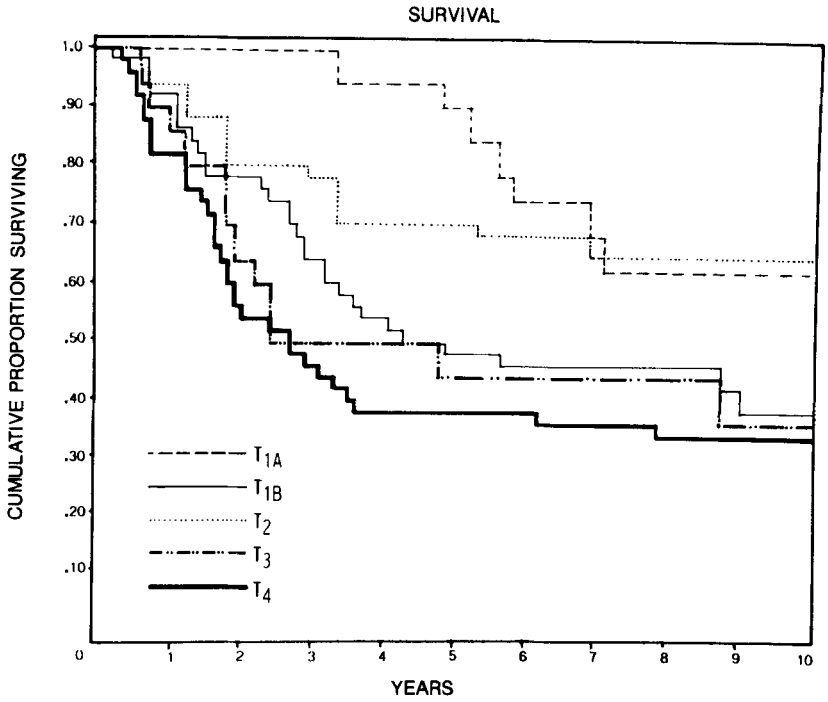

Fig. 3. Survival rate considering death from all causes of patients with T1(n=65), T2(n=31), T3(n=20) and T4(n=49) epidermoid carcinoma of the supraglottic larynx treated by radiation therapy. All patients had a clinically negative neck (No).

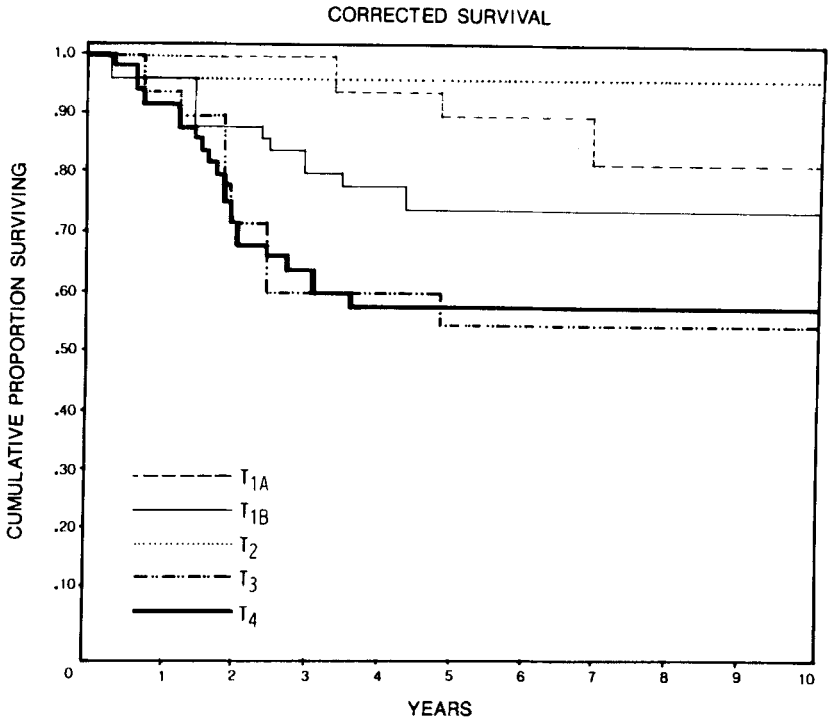

Fig. 4. Corrected survival rate considering death due to epidermoid carcinoma of the supraglottic larynx only for patients with T1(n=65), T2(n=31), T3(n=20) and T4(n=49) tumors treated by radiation therapy. All patients had a clinically negative neck (No).

been radiation therapy (3, 4, 9, 13), surgery (5, 6, 26) or combined modality therapy (10, 11, 12, 14), partly depending on stage and/or the treatment philosophy of the different cancer centers.

We have adopted the concept of conservation treatment by primary radiation therapy, thereby preserving speech; however, surgery remains an integral part of the management of tumors less responsive to radiotherapy or as salvage of failures. Cervical nodal metastases are not an infrequent cause of relapse and death from cancer. This paper deals specifically with the ultimate relapse rate in the clinically negative neck and its impact on survival for patients treated with curative intent by radiation therapy only. Our data suggest 3 factors that influence the risk of regional relapse: involvement of the aryepiglottic fold, elective radiation of the neck as measured by size of the radiation field, and local failure (Table 4).

Our finding of an increased risk of a regional relapse for patients with an involved aryepiglottic fold might be a chance finding. Only one of the 8 subregions analyzed showed a marginally significant association. A correction for multiple testing would label the association as statistically non-significant. However, our finding is partly in agreement with Bataini et al. (3) and van den Bogaert et al. (4). Moreover, the influence of inaccurate staging cannot be dismissed. It is for instance well known that tumors located at this subregion are sometimes difficult to stage accurately according to the UICC rules (37). Small tumors on the margin of the aryepiglottic fold, being the boundary of the supraglottic larynx, can easily be called T4 tumors if extending just beyond the larynx.

We have found that small radiation fields have a considerably higher risk of regional relapse which suggests that elective radiation of the neck is effective in reducing the incidence of neck relapse. In clinical practice it is a frequent dilemma whether elective treatment of the neck is justified for all tumor stages. As practically all patients with T3/T4 tumors (63 out of 69) were offered elective RT to the neck, we could not evaluate adequately any relationship between nodal relapse and tumor stage. However, from the literature it is apparent that even small lesions do show a fairly high incidence of nodal relapse (1, 3, 4, 15, 17, 19, 29). Moreover, in the present study 5 out of 12 patients with T1/T2 tumors, after having been radiated to their primary tumor only and remaining locally NED, still experienced a nodal relapse. As we have reported before (15), prevention of nodal relapses remains an essential part of the treatment as a recurrence in the neck carries a poor prognosis; eventually nearly two thirds of these patients die of their disease. In the near future it might become possible to identify non-invasively some patients with a clinically negative neck who harbor subclinical metastases in the lymph nodes. Techniques, such as cytology with CT-guidance and/or echographic control seem promising (34). However, until such techniques prove more reliable, one remains with the fallibility of palpation to determine the presence or absence of nodal metastases (30). Marks & Ogura (17) have pointed out the problem of contralateral metastases. This is in agreement with the present series; i.e. no association was found between the side of the regional relapse and the lateralization of the primary tumor. It has been shown by others that it is not possible to accurately identify surgically patients having occult disease, unless one is prepared to perform bilateral elective neck dissections (2, 15, 25). Moreover, many reports in the literature have suggested the efficacy of elective treatment of both sides of the neck by radiation therapy (3, 9, 12, 13, 21); most authors, however, have stressed the importance of using a sufficient dose (45–60 Gy) for subclinical disease (9, 20, 21). As the treatment has low associated morbidity (32), radiation therapy remains the modality of choice in our department for elective (bilateral) treatment of the neck. It might even be possible to further reduce the neck failure rate by increasing the dose level to 50 Gy.

Our third main finding is that a local relapse increases the risk of a regional failure more than 3-fold. In order to prevent a regional relapse it therefore seems important not only to treat the neck electively but foremost to reduce the incidence of local recurrences. Of the 165 patients, 65 experienced a local recurrence, 5 of which after a regional relapse, i.e., 30% (29/96) with early stage and 52% (36/69) with advanced stage tumors. The ultimate salvage rate of the local-regional relapses in patients with T1/T2 tumors was 67%; in the T3/T4 category only 43% of patients was salvaged. Regarding the lower local control rate and salvage rate of advanced stage supraglottic cancers, advocates of primary irradiation with surgery in reserve may be saving the larynx for some of their patients while losing the lives of others. This could be a reasonable explanation for the disappointing corrected survival data of Harwood et al. (12) (5-year 42%) and of our own series (5-year 55%). Some series have reported better results by surgery in combination with radiation therapy. Kazem et al. (14) for instance, claimed 80% 5-year survival for T3/T4 N0 supraglottic cancer treated by preoperative RT and total laryngectomy. The probability of local control may also depend critically on the number of tumor clonogens and the radiation dose (28, 35, 39). We have not tailored our dose to tumor stage; i.e. the maximum dose varied between 60 and 70 Gy rather independent of tumor stage. Moreover, specifically in the advanced tumors a split period of several weeks was introduced. The use of a standard dose protocol and a variable split period seems somewhat inconsistent with radiobiological data (16, 28) and might also have been a limiting factor in the local tumor control of this series (16). It is possible that the salvage survival rate of patients with T3/T4 tumors could be improved, either by using some form of combined modality treatment and/or by raising the tumor dose to the primary substantially without compromising the normal tissue tolerance.

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