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Cancer of the Larynx

Treatment Results after Primary Radiotherapy with Salvage Surgery in a Series of 1005 Patients

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The aim of this study is to present and discuss the results of initial radiotherapy with salvage surgery and to compare them with those from centres where primary surgery is the prevailing principle. The series comprised 1005 consecutive patients treated during the period 1965–1998. Salvage surgery was performed if patients had residual tumour or developed recurrence. Disease-specific survival (DSS) and crude survival (CS) after 5 years, among 643 patients with glottic carcinomas treated with curative radiotherapy was 88.6% (SE = 1.3) and 65.3% (SE = 2.0), respectively. Among T1 glottic carcinomas the locoregional control was 88%, i.e. 88% of patients were cured after radiotherapy alone, and the DSS was 99%, both evaluated after 5 years, i.e. the salvage surgery added approximately 11% to the survival of T1 glottic patients. Only 4% (12/312) of T1 glottic patients had laryngectomies. Locoregional control among T2 glottic cases was 67% and the DSS 88%, but, 18% (41/233) of patients lost their larynx. The corresponding results among T3 glottic cases were 30% and 59%, i.e. the organ preservation was close to 50%. Among patients with supraglottic carcinomas, the two estimates were 44% and 63%, respectively. Compared with our results, recent results published in the literature after initial laser surgery of T1 glottic carcinomas indicate that there are only minor differences in DSS and organ preservation, but it is generally agreed, but not proven, that voice quality after radiotherapy is better. T2 glottic carcinomas treated by initial supracricoid partial laryngectomy in a selected series have yielded very high DSS rates with better organ preservation than was observed in the present series. As to T3 glottic carcinomas, initial surgery does not produce better survival rates than those produced in the present series but our organ preservation is higher. The treatment of patients with supraglottic carcinoma has benefited from optimization of radiotherapy during recent decades. The role of initial laser surgery is as yet undecided.

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The choice of treatment of laryngeal cancer is a controversial topic even today. Primary surgery is the preferred procedure in the greater part of Europe, particularly in the middle and southern areas. However, primary radiotherapy has been used in Northern Europe for more than half a century; this also applies to Denmark. Improvement in the results following radiotherapy can be traced throughout the last two and a half decades. Both laser equipment and laryngeal preservation procedures have been developed during the same period.

The purpose of the present study is to report and discuss our results after the use of initial radiotherapy followed by salvage surgery and, furthermore, to compare them with those achieved in centres where primary surgery is the prevailing principle.

MATERIAL AND METHODS

The series comprised 1005 consecutive patients (140 females, 865 males), treated with primary radiotherapy at the Centre of Oncology, Odense University Hospital, Denmark during the period 1965–1998. The patients were referred to the centre from four counties, with approximately 1.33 million inhabitants. All of the patients suffered from invasive, squamous cell carcinoma. Mean age at the time of histological diagnosis was 63.4 years (range 16–97).

Symptoms and signs

Of the patients with glottic carcinoma, 97.2% stated that hoarseness was the first symptom, whereas only 50.7% of patients with supraglottic carcinoma found that hoarseness was the initial symptom. The second most common symptom in the latter group was irritation and pain in the throat. No less than 29% of patients complained of this symptom.

Location of the carcinomas

The site of origin was the supraglottic region in 339 (33.7%) patients, the glottic region in 654 (64.9%) patients and the subglottic area in 12 (1.2%) patients (Table 1).

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Table 1

Site of origin

	No.	%
Suprahyoid epiglottis	102	10.1
Aryepiglottic fold, laryngeal aspect	59	5.9
Arytaenoid	7	0.7
Infrahyoide epiglottis	49	4.9
Ventricular bands	122	12.1
Vocal cords	649	64.5
Anterior commissure	4	0.4
Posterior commissure	1	0.1
Subglottis	12	1.2

Classification

All of the patients were classified according to the criteria of the UICC from 1982 (1). As a consequence, the patients in the early part of the series were reclassified. The main principles of the classifications have been almost the same over the whole period. The analyses were based on the stage of the disease, as well as on the occurrence of lymph node metastases. Table 2 outlines the distribution of the series in respect of stage of disease. Lymph node metastases were more common among patients with supraglottic carcinoma: 29.8% (101/339) in contrast to patients with glottic carcinoma, where only 1.4% (9/654) had lymph node involvement when first seen.

Treatment

Of the 1005 patients included in the study, 990 were offered initial radiotherapy; 981 of these patients completed treatment with curative intent, while 9 were treated with palliative intent. Fifteen patients were subjected to primary surgery: 3 partial laryngectomies; 7 total laryngectomies; 5 neck dissections; 2 patients who had neck dissections also underwent pharyngectomy with reconstruction. The indication for primary surgery was usually previous malignant disease treated with radiotherapy, including neck and verrucous carcinoma, thought to be radioresistant. Cobalt 60 high voltage radiotherapy was used from 1965 to 1985 at which time linear accelerators took over, using 4-6 MV x-rays. Lateral opposed fields were used on almost all patients, with both fields being treated at each session, using 5 fractions per week. A shell for fixation during treatment was produced for each patient and a simulator was used for accurate positioning and size of the fields. Small tumours without lymph node metastases were

Table 2

Stage of disease

	Supraglottic	Glottic	Subglottic
St1	65	315	
St2	52	234	5
St3	105	82	
St4	117	23	7

treated almost exclusively using 6×6 cm fields. The field size was extended in cases where there were larger tumours and lymph node metastases in the neck. The magnitude of the central tumour doses was increased gradually during the period. Subclinical disease was treated with a dose of 48–50 Gy. Prior to 1977 small tumours received 57 Gy over 6 weeks in 30 fractions. The central tumour doses were between 62 and 66 Gy in the last decennium, depending on the stage of the disease. Various patterns of fractionation and modifications of treatment as well as different radiosentitizers have been used during the 33 years' study period. Stage 3 and 4 patients were given induction chemotherapy for a short period some 20 years ago. The Oncological Centre in Odense has participated in several national trials, i.e. DAHANCA-studies (the Danish Head and Neck Cancer Study), and subsequent to 1979 the majority of patients have been enrolled in these randomized studies. Details concerning the oncological treatment can be found in the publications of the DAHANCA group (2–8).

Salvage surgery was performed if the patients had residual tumour or developed recurrence. Either partial or total laryngectomy was performed in cases of tumours in the T-position, while tumours in the N-position were treated with neck dissection. Total laryngectomy and pharyngectomy with reconstruction by means of a free jejunal graft or forearm flap were performed in cases with considerable tumour extension into the larynx and hypopharynx.

Follow-up

The patients were followed for 10 years, until 1990. Thereafter the patients were followed for at least 5 years; in the first 3 years at intervals of 2–4 months, and from 3 to 5 years every 6 months. Three patients were lost to follow-up. After 1995 all patients with supraglottic carcinomas had ultrasonography of the neck in the first 2 years after radiotherapy.

All data on patients treated between 1965 and 1977 were registered retrospectively in the database. All information has been gathered prospectively since 1977. Up until 1992, data were registered in a database using the Fortran program language. All data were transformed into the data management and analysis system, Medlog, in 1992. Survival curves were calculated using the Kaplan-Meier method (9). Disease-specific survival (DSS) was calculated using 'death from laryngeal cancer' as the endpoint and crude survival (CS) using 'death from all causes' as the endpoint. Locoregional control after radiotherapy was also calculated as Kaplan-Meier plots using local and regional failure after radiotherapy as the endpoint. Figures including both DSS and locoregional control have been produced in order to estimate the benefit of salvage surgery. The difference between these curves illustrates the influence of salvage surgery. A few reservations about this

procedure should be mentioned. The difference is not reasonably exact until 5 years of follow-up because nearly all recurrences occur during the first 3 years of observation and it is likely that patients not receiving any treatment for their failure after radiotherapy will die before two years have elapsed. Another reservation is that only insignificant frequency of remote metastases must be present. All survival calculations are based on updated information from the National Register as of 1 October 2000. Tabulated data are based on χ^2 statistics or the Fisher's exact test; all p-values are two tailed.

RESULTS

Change in the appearance of the disease?

The series was examined for changes in gender, histology, mean age, stage of disease and symptomatology during the period under study (34 years). No changes could be observed apart from an increase in the female proportion: before 1 July 1981 the females constituted 9.7%, and thereafter 13.9% ($p = 0.007$).

Representative series?

Up until 1997 the catchment area comprised three counties with close to 1 million inhabitants. A further county was added after 1997, increasing the catchment area to 1.33 million. The occurrences of the disease in these four counties were very close to one another. During the summer of 2000, cross-checking with The Danish Cancer Registry resulted in an additional 14 patients being included in the series. Patients referred to centres outside the catchment area were not identified. Hence, the series can be regarded as being close to representative of the occurrence of laryngeal cancer in four Danish counties with 1.33 million inhabitants.

Survival of all patients

As mentioned, 15 patients were subjected to surgery as the primary treatment and 9 patients were given radiotherapy for palliation. These 24 patients are included in the survival calculations in Fig. 1 only, which shows the estimates of DSS and CS among all 1005 patients. The DSS was 78.5% (SE = 1.4) and the CS 54.9% (SE = 1.7) after 5 years of follow-up.

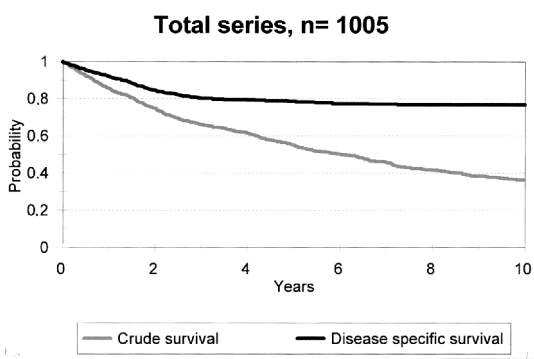

Fig. 1. Disease-specific and crude survival in series of 1005 patients with invasive laryngeal carcinoma.

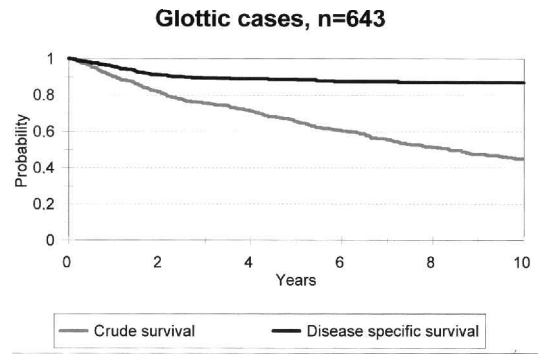

Fig. 2. Disease-specific and crude survival among 643 patients with glottic carcinoma treated with primary irradiation.

Results in patients with glottic carcinomas

Estimates of the DSS and the CS among 643 patients with glottic carcinoma having curative radiotherapy are presented in Fig. 2. After 5 years the DSS was 88.6% (SE = 1.3), and the CS 65.3% (SE = 2.0). In Fig. 3 it is shown that among T1 glottic carcinomas the locoregional control was 88%, i.e. 88% were cured after radiotherapy alone and that the DSS was 99%, both evaluated after 5 years. The difference between the curves expresses the benefit gained from salvage surgery, which adds approximately 11% to the survival of T1 glottic patients. The corresponding numbers in respect of patients with T2, T3 and T4 carcinomas are presented in Figs. 4–6. The 5-year estimates can be found in Table 3. Laryngeal preservation after salvage surgery may be expressed using the ratio between partial and total laryngectomy, performed as salvage surgery. Among T1 glottic carcinomas, the ratio was 21/12. This means that only 4% (12/312) of patients lost their larynx. For T2 cases, the corresponding ratio was 20/41 and total laryngectomy was performed in 18% (41/233) of

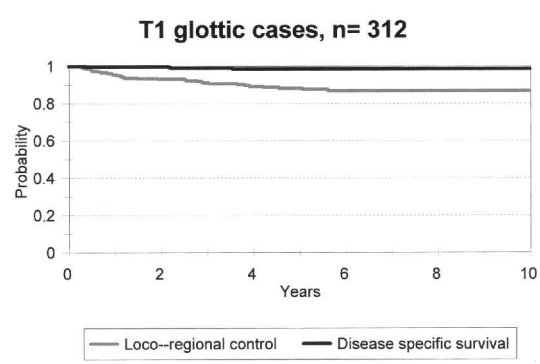

Fig. 3. Disease-specific survival and locoregional control after radiotherapy among 310 patients with T1 glottic carcinoma.

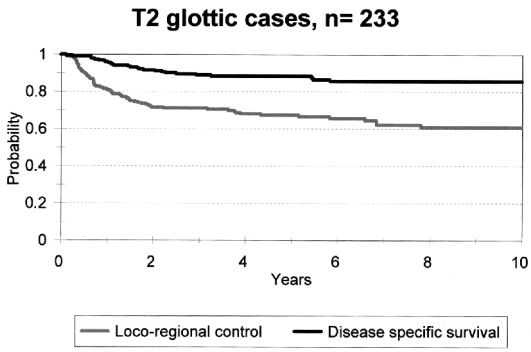

Fig. 4. Disease-specific survival and locoregional control after radiotherapy among 233 patients with T2 glottic carcinoma.

the patients. Almost half of the patients with T3 glottic carcinomas lost their larynx (Table 3, Fig. 5). Salvage surgery entailed total laryngectomy, apart from a couple of neck dissections.

Results in patients with supraglottic carcinomas

The analysis of this group of patients was carried out in the same manner as that for the glottic group and is presented in Fig. 7; in addition, Table 3 gives the 5-year estimates.

Surgical results

Salvage surgery (250 patients) was carried out on all patients where their medical condition permitted. A total of 250 patients were operated on; the 291 procedures included 48 partial laryngectomies (44 vertical and 4 horizontal), 190 total laryngectomies, 50 neck dissections and 3 stoma recurrence operations.

The prognosis of patients treated with salvage surgery was evaluated separately. The estimates for DSS and CS after 5 years were 65.6% and 49.5%, respectively. Three recurrences following partial laryngectomy were treated with extended partial laryngectomy in two patients and one partial laryngectomy was converted into a total laryngectomy.

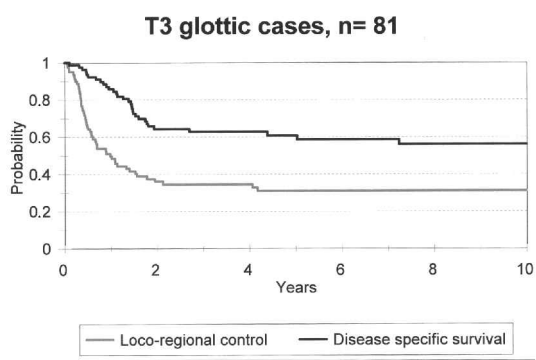

Fig. 5. Disease-specific survival and locoregional control after radiotherapy among 81 patients with T3 glottic carcinoma.

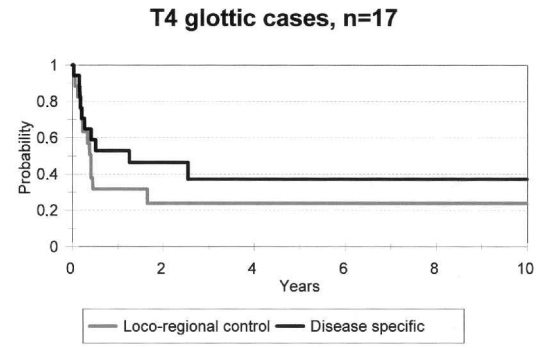

Fig. 6. Disease-specific survival and locoregional control after radiotherapy among 17 patients with T4 glottic carcinoma.

Improvement during the 34-year period?

The patients in this series are registered in two databases, an older base from before 1992 and a new modernized version after 1992. The analysis compared the DSS, the locoregional control after radiotherapy and CS in the two databases among patients with glottic and supraglottic carcinomas. Table 4 contains the observed estimates and hence reveals the changes ($p > 0.05$ evaluating all observed differences).

Complications

All patients had varying degrees of oedema and mucositis during and after radiotherapy. The need for tracheotomy during treatment has been registered since 1992. Five patients underwent this procedure—the tracheotomy was only temporary in all cases and none of the patients had a tracheotomy owing to late persistent reactions. In this series some of the patients with supraglottic carcinomas developed moderate persistent xerostomy. No special evaluation of the voice quality was made. A small group of the patients had persistent severe dysphonia. Initially, all of these patients had large destructive tumours, which can explain the condition. The habitual voice quality did not return in any of the patients, but voice deterioration was minimal in the vast majority.

Table 3

Estimates of 5-year disease-specific survival and locoregional control following radiotherapy and 5 years of follow-up among 643 patients with glottic carcinoma and 327 with supraglottic carcinoma

Stage of disease	Estimated 5-year disease-specific survival (%)	Estimated 5-year locoregional control after RTH (%)
T1 glottic cases	98.8	88.1
T2 glottic cases	88.4	67.4
T3 glottic cases	58.6	30.5
T4 glottic cases	37.1	23.8
Supraglottic cases	62.8	43.9

RTH = radiotherapy.

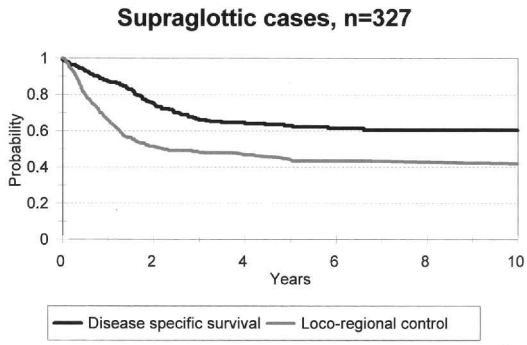

Fig. 7. Disease-specific survival and locoregional control after radiotherapy among 327 patients with supraglottic carcinoma.

The most important surgical complication–pharyngocutaneous fistula–was seen in 49 out of 197 total laryngectomies, giving a frequency of fistulas of 25%. This frequency was 27% (41/153) before 1992 and 18% after that time (8/44) ($p > 0.05$). Three patients developed stenosis of the larynx after partial laryngectomy. Two of these patients were decannulated after laser surgery and one patient had a permanent cannula.

DISCUSSION

The basic data of our series do not reveal any new changes. The occurrence of the disease has changed only with regard to the female/male ratio, which we found to have increased significantly. Two different rules of classification have been used during the period of registration. Reclassification was carried out according to the rules from 1982 (1), at which time identical systems of classifications were adopted in both America and Europe. The series is unselected and almost representative of the disease in a well-defined geographical area.

The treatment policy—primary radiotherapy with salvage surgery—has been constant throughout the period under study and this permits analysis of the series as a whole. Several explanations can be given for our conservatism as to primary treatment. Half a century ago the Danish Societies of Oto-Rhino-Laryngology and Oncology agreed upon the principle of using primary radiotherapy for laryngeal and pharyngeal cancer. Furthermore, most treatment procedures have been protocolated in the DAHANCA studies dealing with modifications of radiotherapy (2–8). This does not mean that we are not aware of new aspects in treatment based on technological development—especially the laser technique. Indeed, one of the reasons for this analysis has been to determine whether there is a need for changing our treatment policy. A few patients in this series have been treated with induction chemotherapy according to the first DAHANCA protocol (3), but no positive effect could be traced. More than 70 randomized trials have been published in the literature but no clear conclusions have been drawn so far (10).

Treatment of T1 glottic carcinomas

It can be seen from the literature that a majority of authors prefer primary radiotherapy (11–15). However, initial surgery—either laser surgery or modified partial laryngectomy—has its advocates, primarily because of the technical and surgical developments (16–19). The cure rate and larynx preservation are equally high, regardless of primary treatment. The crucial point, however, is voice quality. Most authors agree that laser surgery results in a deterioration of voice quality (20, 21). A dysphonia severity index (DSI) (22) has been formulated in recent years but no international agreement has been reached so far. However, the formulation of a DSI is promising and an international agreement may lead to a simple way of performing trials with comparison of different treatment modalities.

There are few reports in the literature concerning recurrences after primary laser therapy. Eckel (23) reported a recurrence rate of 13% in a large series. It can be seen from Table 3 that we had a recurrence rate of 12% after 5 years following radiotherapy. However, two-thirds of the salvage surgery entailed partial laryngectomies and the end result was a high cure rate and organ preservation where only 4% of the patients were subjected to total laryngectomy. It seems that there are certain reservations concerning the use of partial laryngectomy as a salvage procedure

Table 4

Patients treated before of 1 Jan. 1992 compared with patients treated after this date

	Before 1 Jan. 1992	After 1 Jan. 1992
Glottis		
Disease-specific survival 3 years of follow-up	89.8	92.6
Locoreg. control following RTH after 3 years of follow-up	74.6	81.0
Crude survival, 3 years of follow-up	75.1	75.9
Supraglottis		
Disease-specific survival, 3 years of follow-up	65.0	68.0
Locoreg. control following RTH after 3 years of follow-up	45.3	52.7
Crude survival, 3 years of follow-up	52.4	49.4

Abbreviations: Locoreg. = loco/regional; RTH = radiotherapy.

(12, 19, 24–26). We consider that no change can be justified in our treatment policy in this group of patients.

Treatment of T2 glottic carcinomas

With regard to the results in the T2 group, we found that the locoregional control after radiotherapy was significantly lower compared with the findings in the T1 group. One-third of the patients with T2 tumours developed recurrence after radiotherapy, i.e. the locoregional control was 67% (Table 3) and in two-third of cases the salvage surgery was total laryngectomy. The final result shows a DSS of 90%, with preservation of the larynx in 80% of the patients. This result does not differ from data published from other centres with the same treatment policy (12, 14, 27). However, other treatment modalities must be considered. Supracricoid partial laryngectomy used initially (28) has produced remarkable results, with 96% DSS and 95% locoregional control and organ preservation. The voice quality after radiotherapy is definitely considerably better than that after supracricoid partial laryngectomy. However, the above-mentioned three parameters are on a better level than those in our series. Why not introduce supracricoid partial laryngectomy as primary standard treatment of T2 glottic carcinomas? The patients in the study by Chevalier et al. (28) were gathered from two institutions and hence to some extent are selected. Furthermore, optimization of radiotherapy seems to have improved the results in our series during recent years (Table 4). Therefore we find it acceptable to continue our usual procedure using primary radiotherapy.

Supracricoid partial laryngectomy has been used as salvage surgery. Whereas experience of the operation used as primary treatment is promising (28), experience with this type of operation as salvage surgery after radiotherapy is scarcer and less optimistic (29) perhaps owing to a high rate of complications. Using supracricoid partial laryngectomy as salvage surgery may lead to a higher rate of larynx preservation, and, despite the difficulties, it is likely that in the future this type of surgery will be used more extensively as salvage surgery (19).

Treatment of glottic T3 carcinomas

Large oncological centres have reported results after primary radiotherapy that are comparable with ours (30, 31). One of these, a Swedish analysis of 600 patients treated for T3 or T4 glottic carcinomas, revealed that patients with T3 tumours having primary radiotherapy with salvage surgery did better than patients having initial total laryngectomies. Recently, Tucker (32) published the results of treating 132 patients with T3 glottic carcinomas with initial surgery. A total laryngectomy was performed on 69% of the patients and in 31% different types of extended partial or subtotal laryngectomy. Tucker's paper did not include any information on survival. In our series (Table 3) primary radiotherapy with salvage surgery resulted in a DSS of 58% with a laryngeal preservation rate in the survivors of almost 50%. However, it cannot be denied that the recurrence rate after radiotherapy is very high. Further optimization of radiotherapy or selection of patients with a poor chance of cure by radiotherapy for primary surgery is possible. The present DAHANCA project evaluates the optimization of radiotherapy among patients with glottic carcinomas. A safe method of selecting patients with little chance of cure after radiotherapy for initial surgery does not exist so far (30).

At present, the role of initial supracricoid partial laryngectomy among patients with T3 glottic carcinomas is unknown. Tucker (32) reported that this procedure was possible in about one-third of the patients. Chevalier and colleagues (28) state in their paper that it could be performed in selected cases. We find that there is no clear indication in the literature that a change is needed in our treatment policy.

Treatment of glottic T4 carcinomas

The results of our study concerning patients withT4 glottic carcinomas are poor. To some extent, T4 patients resemble patients with hypopharyngeal cancer (33). The proportion of patients with hypopharyngeal cancer having only palliative treatment because of poor health is high. As mentioned earlier, only 9 out of 990 patients in this series had radiotherapy for palliation and 6 of them had glottic T4 carcinomas. For many years initial surgery in hypopharyngeal cancer has been discussed. Could primary surgery in patients with T4 glottic carcinomas be considered? The Swedish analysis mentioned above (31) gave a strong indication that patients having initial surgery had a better prognosis than those subjected to primary radiotherapy. However, it is a retrospective analysis that does not exclude the possibility that some patients were selected. Patients with a good performance status might have been selected for initial surgery. Hence, the question as to initial surgery of T4 cases is unanswered and still open.

Treatment of supraglottic carcinomas

The DAHANCA trials have introduced modifications to conventional radiotherapy. We are now using accelerated fractionation and the radiosensitizer, Nimorazole. The trials have significantly improved the nationwide treatment results (3–8), which can also be seen from the results at our centre (Table 4). In Table 3 it is shown that salvage surgery actually accounts for about 20% of the observed disease-specific survival. A new surgical laser technique for initial treatment of supraglottic carcinomas has been introduced during the past two decades (34) and is now being used at some centres. It should be pointed out that careful selection is important and hardly more than 20% of supraglottic cases are suitable for this type of surgery. Some prefer prophylactic neck dissection combined with laser therapy, while others prefer radiotherapy. We conclude

that the role of laser surgery in the primary treatment of supraglottic cases has not been clarified so far, and there is nothing at present to indicate that a change in treatment policy would be advantageous.

Lymph node metastases were clinically present in 30% of patients with supraglottic carcinomas in our series and about 20% of patients had subclinical metastases. The treatment fields in radiotherapy include the regional lymph node stations and, hence, a considerable number of patients have prophylactic treatment of subclinical lymph node metastases. The introduction of accelerated radiotherapy has not lead to increased cure and for this reason the number of neck dissections performed in this series has not decreased.

Salvage surgery

The prognosis after salvage surgery is good. The level of complications is acceptable; in fact, the number of pharyngo-cutaneous fistulas decreased after 1992 during a period with unchanged central tumour doses of irradiation and introduction of more intensive regimes.

Conclusion

We have treated 1005 patients with laryngeal carcinoma over a period of 34 years and 98% of patients received initial radiotherapy. The level of results evaluated by the patients' cure and preservation of laryngeal function is acceptable and close to that found in the recent literature. However, new modalities in both primary and salvage treatment deserve attention and we will continue to evaluate and develop our treatment policy.

REFERENCES

1. UICC. TNM classification of malignant tumours. Genova. 1982.
2. Hansen HS, Rygard J, Andersen AP, et al. Bleomycin, methotrexate and vincristine before irradiation of stage III and IV laryngeal and pharyngeal squamous cell carcinoma. A study initiated by the Danish Society of Head and Neck Cancer. Acta Oncol 1987; 26: 13–8.
3. Overgaard J, Hansen HS, Andersen AP, et al. Misonidazole combined with split-course radiotherapy in the treatment of invasive carcinoma of larynx and pharynx: report from the DAHANCA 2 study. Int J Radiat Oncol Biol Phys 1989; 16: 1065–8.
4. Overgaard J, Hansen HS, Lindelov B, Overgaard M, Jorgensen K, Rasmusson B. Nimorazole as a hypoxic radiosensitizer in the treatment of supraglottic larynx and pharynx carcinoma. First report from the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85. Radiother Oncol 1991; 20 (Suppl 1): 143–9.
5. Overgaard J, Hansen HS, Overgaard M. The Danish Head and Neck Cancer Study Group (DAHANCA), randomized trials with hypoxic radiosensitizers in carcinoma of the larynx and pharynx. In: Dewey WC, Edington M, Fry RJM, et al., eds. Radiation research: a twentieth-century perspective, vol. 2. New York: Academic Press, 1992: 573–7.
6. Hansen HS, Overgaard J, Overgaard M, et al. Continuous versus split-course radiotherapy of advanced supraglottic carcinoma-experience from the Danish Head and Neck Cancer Study (DAHANCA). In: Smee R, Bridger GP, eds. Laryngeal Cancer. Amsterdam: Elsevier Science, 1994: 539–43.
7. Overgaard J, Hansen HS, Overgaard M, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85. Radiother Oncol 1998; 46: 135–46.
8. Overgaard J, Hansen HS, Overgaard M, et al. Importance of overall outcome of radiotherapy in head and neck carcinoma. Experience from the Danish Head and Neck Cancer Study. Prog Radio-Oncol VI 1998; 1: 743–52.
9. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Am Stat Ass J 1958; 1: 457–81.
10. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet 2000; 355: 949–55.
11. Fernberg JO, Ringborg U, Silfversward C, et al. Radiation therapy in early glottic cancer. Analysis of 177 consecutive cases. Acta Otolaryngol 1989; 108: 478–81.
12. Schwaab G, Mamelle G, Lartigau E, Parise O, Wibault P, Luboinski B. Surgical salvage treatment of T1/T2 glottic carcinoma after failure of radiotherapy. Am J Surg 1994; 168: 474–5.
13. van der Voet JC, Keus RB, Hart AA, Hilgers FJ, Bartelink H. The impact of treatment time and smoking on local control and complications in T1 glottic cancer. Int J Radiat Oncol Biol Phys 1998; 42: 247–55.
14. Warde P, O'Sullivan B, Bristow RG, et al. T1/T2 glottic cancer managed by external beam radiotherapy: the influence of pretreatment hemoglobin on local control. Int J Radiat Oncol Biol Phys 1998; 41: 347–53.
15. Grant DG, Hussain A, Hurman D. Pre-treatment anaemia alters outcome in early squamous cell carcinoma of the larynx treated by radical radiotherapy. J Laryngol Otol 1999; 113: 829–33.
16. Steiner W. Results of curative laser microsurgery of laryngeal carcinomas. Am J Otolaryngol 1993; 14: 116–21.
17. Rudert H, Werner JA. Partial endoscopic resections with CO_2 laser in laryngeal cancer. I. Resection techniques. Laryngorhinootologie 1994; 73: 71–7.
18. Moreau PR. Treatment of laryngeal carcinomas by laser endoscopic microsurgery. Laryngoscope 2000; 110: 1000–6.
19. Ferlito A, Silver CE, Howard DJ, Laccourreye O, Rinaldo A. The role of partial laryngeal resection in current management of laryngeal cancer: a collective review. Acta Otolaryngol Stockh 2000; 120: 456–65.
20. Hirano M, Ohkubo H, Kurita S, et al. CO_2 laser in treating carcinoma of the tongue. Auris Nasus Larynx 1985; 12 (Suppl 2): 10–4.
21. Rydell R, Schalen L, Fex S, Elner A. Voice evaluation before and after laser excision vs. radiotherapy of T1A glottic carcinoma. Acta Otolaryngol 1995; 115: 560–5.
22. Wuyts FL, De BM, Molenberghs G, et al. The dysphonia severity index: an objective measure of vocal quality based on a multiparameter approach. J Speech Lang Hear Res 2000; 43: 796–809.
23. Eckel HE. Local recurrences following transoral laser surgery for early glottic carcinoma: frequency, management and outcome. Ann Otol Rhinol Laryngol 2001; 110: 7–15.

24. Jose B, Calhoun DL, Mohammed A. Recurrences after irradiation in early vocal cord cancer with literature review. J Surg Oncol 1984; 27: 224–7.
25. Maipang T, Razack MS, Sako K, Chen TY. Surgical salvage for recurrent 'early' glottic cancers. J Surg Oncol 1989; 40: 32–3.
26. Suzuki H, Hasegawa T, Sano R, Kim Y. Results of treatment of laryngeal cancer. Acta Otolaryngol 1994; 511: 186–91.
27. Howell-Burke D, Peters LJ, Goepfert H, Oswald MJ. T2 glottic cancer. Recurrence, salvage, and survival after definitive radiotherapy. Arch Otolaryngol Head Neck Surg 1990; 116: 830–5.
28. Chevalier D, Laccourreye O, Brasnu D, Laccourreye H, Piquet JJ. Cricohyoidoepiglottopexy for glottic carcinoma with fixation or impaired motion of the true vocal cord: 5-year oncologic results with 112 patients. Ann Otol Rhinol Laryngol 1997; 106: 364–9.
29. Laccourreye O, Weinstein G, Naudo P, Cauchois R, Laccourreye H, Brasnu D. Supracricoid partial laryngectomy after failed laryngeal radiation therapy. Laryngoscope 1996; 106: 495–8.
30. Lundgren J, Gilbert R, Nostrand AW, Harwood AR, Keane TJ, Briant TD. T3N0M0 glottic carcinoma—a failure analysis. Clin Otolaryngol 1988; 13: 455–65.
31. Finizia C, Geterud A, Holmberg E, et al. Advanced laryngeal cancer T3-T4 in Sweden: a retrospective study 1986–1990. Survival and locoregional control related to treatment. Acta Otolaryngol Stockh 1996; 116: 906–12.
32. Tucker HM. Exploratory' surgery for advanced carcinoma of the larynx: a relatively safe approach. Ann Otol Rhinol Laryngol 1998; 107: 388–90.
33. Johansen J, Christensen PH, Jørgensen K, Andersen JE. Epidermoid carcinoma of the pharynx. Therapeutic results in 151 patients. Acta Oncol. 1991; 30: 30–7.
34. Rudert HH, Werner JA, Hoft S. Transoral carbon dioxide laser resection of supraglottic carcinoma. Ann Otol Rhinol Laryngol 1999; 108: 819–27.