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TREATMENT OUTCOME WITH T3N0-1 LARYNGEAL CARCINOMAS: PRIMARY RADIOTHERAPY VERSUS SURGERY WITH PRE-/POSTOPERATIVE RADIOTHERAPY

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Abstract Treatment outcome was evaluated for twenty-three patients with previously untreated T3N0-1 squamous cell carcinomas of the larynx, with special attention to laryngeal voice preservation. Fifteen patients underwent primary radiotherapy reserved for surgical salvage (PRT), and eight patients underwent surgery with pre-/postoperative radiotherapy (SR). The overall 5-year cumulative survival rate was 55%, and the overall 5-year cumulative cause specific survival rate was 76%. There were no statistically significant differences between the PRT and SR groups, with respective 5-year cumulative survival rates of 66% and 39%, and for respective 5-year cumulative cause specific survival rates of 76% and 73%. Laryngeal voice preservation rates at 5-years follow-up were 62% and 0%, respectively. The results of this study suggest that PRT with high rate of laryngeal voice preservation should be the first choice for the management of T3N0-1 laryngeal carcinomas.

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Key words : Laryngeal cancer ; T3N0-1 staged ; Primary radiotherapy ; Laryngeal voice preservation.

T3N0-1 喉頭癌の治療成績：根治的放射線治療と手術および術前・後放射線照射併用治療の比較

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抄録 T3N0-1 喉頭扁平上皮癌初回治療症例23例の治療成績を喉頭音声温存の可能性を中心に検討した．治療は，15例が根治的放射線治療（PRT），8例が手術および術前・後放射線治療併用（SR）によって行われた．全23例の5年累積生存率（CS）は55%，5年累積原因特異的生存率（CCSS）は76%であった．CS と CCSS に関して，PRT および SR 群間で統計学的有意差は認められなかった．PRT および SR 群の5年 CS は各々66%，39%であり，5年 CCSS は各々76%，73%であった．一方，5年喉頭音声温存率は，PRT および SR 群で各々62%，0%であった．以上の結果は，T3N0-1 喉頭癌の治療においては，高率に喉頭音声温存を期待できる PRT をまず治療の選択肢として検討すべきであることを示している．

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Introduction

As a management option for T3 laryngeal carcinomas, surgery with postoperative irradiation has been reported to have advantages for locoregional control and survival over surgery alone or primary radiotherapy[1~6]. On the other hand, primary radiotherapy is obviously superior to surgery, implying removal of the larynx, in allowing voice preservation[5,7~12]. Therefore, controversy exists with regard to the best treatment strategy for managing T3 laryngeal carcinomas[9].

In the present study, we compared treatment outcome with T3N0-1 laryngeal carcinomas in our institutions, after primary radiotherapy or surgery with pre-/postoperative radiotherapy, to cast light on the optimal treatment strategy for the affected patients.

Materials and Methods

Twenty-three patients received radiotherapy with curative intent for previously untreated T3N0-1 (UICC, 1987[13]) squamous cell carcinoma of the larynx at Hirosaki University Hospital or Aomori Prefectural Central Hospital between July 1985 and July 1996. The series comprised 22 males and 1 female, ranging in age from 45 to 81 years with a median of 65. Fifteen cases had glottic and 8 supraglottic carcinomas. Six patients with glottic and 2 with supraglottic carcinomas had single clinically positive neck nodes.

Fifteen patients were treated with primary radiotherapy (PRT), reserved for salvage surgery. Eight patients were treated surgically, with total laryngectomy and radical neck dissection, in combination with pre- or postoperative radiotherapy (surgery with radiotherapy: SR). With the exception of nodal status, there were no significant differences as to background (age, gender, performance status, and site) between the two groups (Table 1). Radiotherapy was given with a telecobalt unit (Shimadzu, Kyoto) for 10 patients and 4 MV X-rays (Mitsubishi, Tokyo) for 13. All patients were immobilized with plastic head shells prepared for each individual. Computer-generated dosimetry was performed using Thelac (NEC, Tokyo), Modulex (CMS, St. Louis) or Focus (CMS, St. Louis).

Using two parallel opposed portals, initial radiation fields for the PRT group included primary tumors together with cervical lymph nodes even in negative node cases. In two patients who had clinically positive nodes, lower cervical and supraclavicular lymph node areas were also irradiated with a separate anterio-posterior portal. The following reduced fields encompassed a volume including the tumor bearing area. In 13 patients of the PRT group, a conventional fractionated schedule (CF) with a fractionation of 200 cGy five times weekly was employed, except for one case using a fractionation of 250 cGy five times weekly only for the initial fields. Total target doses delivered ranged from 6,800 to 7,000 cGy (median, 7,000 cGy): a target dose of 4,000 to 5,000 cGy was delivered for the initial fields and of 2,000 to 3,000 cGy for the reduced fields. In two patients, a second-half accelerated hyperfractionated schedule (AHF) comprising a conventional first-half 4,000 cGy for the initial fields and a twice-daily second-half of 3,000 cGy using a fractionation of 150 cGy 10 times weekly for reduced fields was employed, resulting in a total target dose of 7,000 cGy. For two patients of the SR group, a total target dose of 3,000 or 4,000 cGy with CF was delivered preoperatively to the whole neck. For other 6 patients of the SR group, a total target dose of 5,000 cGy with CF was deliver-

Table 1 Comparison of backgrounds between primary radiotherapy (PRT) and surgery with pre-/postoperative radiotherapy (SR) cases

Factor	PRT (n=15)	SR (n=8)
Age (years)*	50-81 (68)	45-77 (66)
Gender (M/F)	14/1	8/0
Performance status	1-2	1-2
Site (Glottis/Supraglottis)	10/5	5/3
Nodal status (N0/N1)**	13/2	2/6

*Range with median value in parenthesis.
**According to the UICC TNM classification (1987)[13].

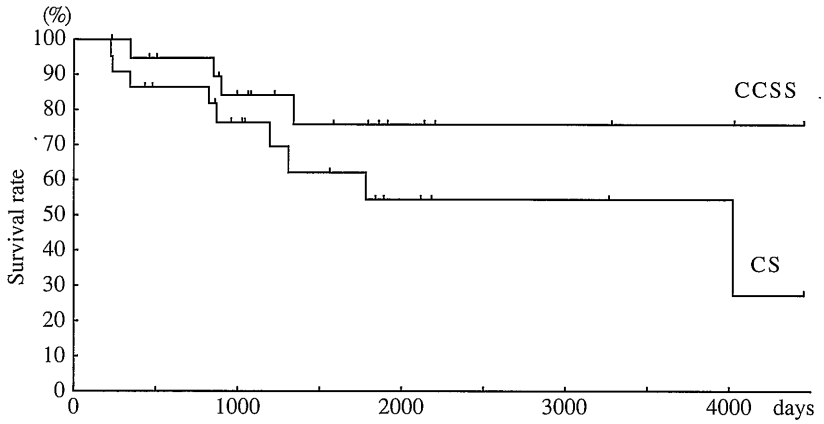

Figure 1 Overall cumulative survival rate (CS) and overall cumulative cause specific survival rate (CCSS) (n=23).

ed postoperatively to the whole neck and supraclavicular fossae.

In 10 patients, adjuvant intensive chemotherapy was also applied. Intra-arterial one shot injection of chemotherapeutic agents via the superior thyroid artery by Seldinger's method[14] was employed for 9 patients. In the first or second week of radiotherapy, 70-80 mg/body of cisplatin (8 cases) or 400 mg/body of carboplatin (one case) and pepleomycin at 5 mg/body (all 9 cases) were intra-arterially administered. In one patient treated with surgery and postoperative radiotherapy, 100 mg/body of cisplatin was intravenously administered prior to surgery.

Results were evaluated on the basis of the period from the start of radiotherapy. The last follow-up was September 30, 1997 and the minimum follow-up period was 14 months. No patients were lost to follow-up. The cumulative survival rate (CS), cumulative cause specific survival rate (CCSS), loco-regional control probability (LCP), and laryngeal voice preservation rate were used as endpoints, analyzed using the Kaplan-Meier method with the log-rank test for differences between subsets of patients.

Results

The overall 5-year CS was 55%, and the overall 5-year CCSS was 76% (Figure 1). Tumor deaths were observed in 4 patients. Three of these died of loco-regional recurrence, and one of both loco-regional recurrence and distant metastases to the lung and the mediastinum. Other cause deaths were observed in 5 patients: from chronic renal disease (2 cases), cardiovascular disease (one case), intracranial hemorrhage (one case), and adenosquamous carcinoma of the lung (one case). The overall 5-year LCP was 66%, and the overall 5-year ultimate LCP was 76%. Loco-regional recurrence was observed in 7 patients, four undergoing salvage surgery with a success rate of 50% (2/4). One patient underwent palliative radiotherapy with a total dose of 3,000 cGy in 15 fractions.

There were no statistically significant differences in 5-year CS (66% and 39%), CCSS (76% and 73%) and LCP (62% and 73%) between the PRT and SR groups (Figure 2a and 2b). The 5-year laryngeal voice preservation rate was 41% for all patients, and 62% for the PRT group. The figure was zero for the SR group. Age, gender, performance status, original site (glottis/supraglottis), nodal status (N0/N1) and intensive chemotherapy combination did not influence the therapeutic results.

No severe late radiation sequelae were observed in the patients of PRT group, and no severe complications occurred in the SR group.

Discussion

Surgical management, implying initial total laryngectomy, with or without radiotherapy has been regarded as the standard treatment strategy for advanced laryngeal carcinomas[1~5]. However, Mendenhall et al.[11] reported that radiotherapy alone for selected patients with T3 glottic carcinoma resulted in similar loco-regional control and survival rates compared with surgery with or without radiotherapy, while the rates for laryngeal voice

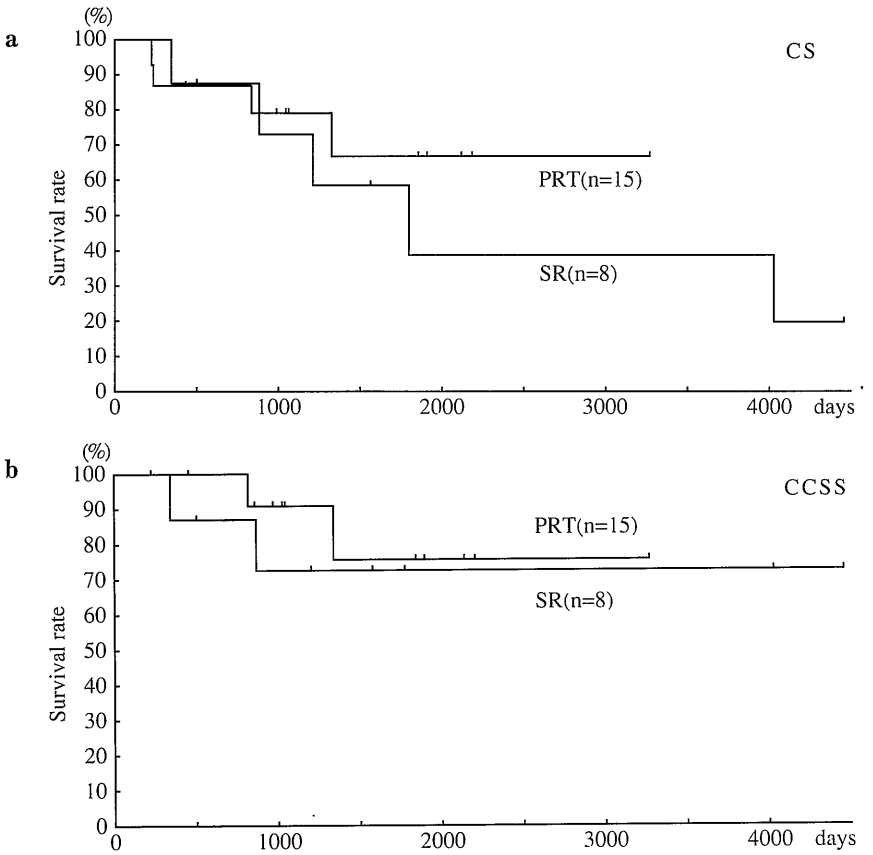

Figure 2 The cumulative survival rate (CS: a) and cumulative cause specific survival rate (CCSS: b) for the two treatment groups: primary radiotherapy (PRT; n=15) and surgery with pre-/postoperative radiotherapy (SR; n=8). There are no statistically significant differences between the groups.

preservation were 66% after radiotherapy alone and only 2% after surgery. Horwood et al.[8] achieved a local control rate of 51% with radiotherapy alone and an ultimate local control rate, including patients successfully salvaged after a local recurrence, comparable with surgery for T3 glottic carcinomas. With T3 supraglottic carcinomas, Mendenhall et al.[10] reported a local control rate of 61% with radiotherapy alone and an ultimate local control rate of 81%. Moreover, Wang[15] demonstrated a 5-year local control rate of 73% for T3-4 supraglottic carcinomas treated with hyperfractionated radiotherapy. In the present study, the treatment results of T3N0-1 laryngeal carcinomas with PRT were also comparable to those for SR. These results indicate that PRT reserved for surgical salvage should be considered as an initial choice for managing patients with T3N0-1 laryngeal carcinomas, especially when preservation of voice and life quality are to be given high priority. Fletcher et al.[16] showed that laryngectomy salvages a high percentage (i.e., 10/11 for T3 lesions of supraglottis) of irradiation failures. Thus treatment choice should be made on the basis of patient's attitudes toward the quality as well as the quantity of survival, as stated by McNeil et al.[9].

For applying PRT to T3 laryngeal carcinomas, careful selection of patients is necessary[5, 11, 17]. A clinico-pathological study[18] showed that a high percentage of irradiation failures with clinically appearing T3N0 lesions were due to masked extralaryngeal spread of disease, underlining the necessity for accurate pretreatment estimation. For patients with T3 glottic carcinoma, high-quality pretreatment CT or MR images contribute to an accurate diagnosis and consequently treatment decisions[17, 19, 20]. Total tumor volume[17, 19] and the extent of laryngeal spread[17] estimated by high-quality CT were found to be well correlated with tumor control by radiotherapy alone. Furthermore,

an ability of MR to identify cartilaginous involvement and thereby to detect masked T4 lesions in T3 cases as diagnosed by CT was recently demonstrated[20]. Thus patient selection for excluding high-risk cases with "T3" lesions might be possible by using high-quality pretreatment CT or MR images, although staging was clinically estimated in the present study.

Regarding the dose fractionation scheme used for T1-2 laryngeal carcinomas, we have demonstrated excellent tumor control with laryngeal voice preservation by AHF schedules[21], in line with several other recent reports for head and neck carcinomas[22,23]. The therapeutic gain with this approach, shortening overall treatment time, is considered due to avoidance of unfavorable influence from accelerated repopulation in tumor clonogenic cells during radiotherapy[21~24]. This positive effect with AHF is more pronounced with T3 than T1-2 tumors[24].

Loco-regional control and survival rates of the patients treated with surgery and pre-/postoperative radiotherapy in the present study were within the range reported in the literature[1~4,6,12,25~27]. However, the total target doses, 3,000-4,000 cGy delivered preoperatively or 5,000 cGy postoperatively, might not have been optimal. Reddi et al.[25] demonstrated that low-dose preoperative radiation therapy with 3,000-3,600 cGy had little effect on supraglottic carcinomas, and a dose of 4,500-5,000 cGy over 5 weeks is recommended for effective preoperative radiotherapy of head and neck carcinoma[26,28]. For postoperative radiotherapy, the possibility of increased tumor resistance as a result of hypoxia, induced by surgical disruption of vascularity and scarring, has been suggested[29]. Hence, a 5,000 cGy dose delivered conventionally, having a control rate of greater than 90% for subclinical disease[30], is considered to be equivalent to a postoperative dose of 6,000 cGy[27]. The loco-regional control of the SR group might have been improved by increasing the total target doses delivered pre-/postoperatively. In turn, as to the optimal sequencing of surgery and radiotherapy, there are advocates of both preoperative and postoperative radiotherapy[27]. Presently, we prefer the preoperative approach, since patients for whom good tumor regression is then observed can be selected, and PRT, leading to laryngeal voice preservation, can be employed for such patients as an alternative to preoperative radiotherapy with surgery[31].

While PRT is not necessarily the best treatment choice for all patients with T3N0-1 laryngeal carcinomas, appropriate selection, based upon high-quality image analysis, as well as predictive assays for tumor radioresponse[32], and application of altered fractionation schemes including AHF[21~23] should increase numbers of successfully-treated cases with laryngeal voice preservation.

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