

Surgical treatment of squamous cell carcinoma of the hypopharynx: analysis of treatment results, failure patterns, and prognostic factors

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Abstract

Patients with squamous cell carcinoma of the hypopharynx (HPSCC) are often seen in advanced stages and have a poor prognosis. The authors analysed 104 patients who had HPSCC and underwent surgery as the primary treatment between 1986 and 1995 in their institute. Of the 104 patients, 83 patients (80 per cent) had advanced T₃ or T₄ staged and 64 patients (62 per cent) had cervical metastasis. Thirteen patients (13 per cent) had conservation surgery with laryngeal preservation and 69 patients (66 per cent) received post-operative radiotherapy. The five-year overall and disease-specific survival was 47 per cent and 62 per cent, respectively. Recurrence occurred in 38 patients (37 per cent), including 12 (12 per cent) with local, 22 (21 per cent) with regional, and 12 (12 per cent) with distant recurrence. Sixteen patients (15 per cent) had recurrence at multiple sites. The site and size of the primary tumour, neck biopsy before surgery, early post-operative complications, and pathological nodal stage were significant prognostic factors of disease-specific survival (DSS) in univariate analysis. Neck biopsy before surgery and site of primary tumour were significant factors in multivariate analysis. In conclusion, surgical treatment for the HPSCC patients has achieved good local-regional control and survival. Bilateral neck dissection for the tumour across the midline and avoiding neck biopsy before surgery may reduce regional recurrence.

Key words: Squamous Cell Carcinoma; Hypopharynx; Surgery; Prognosis

Introduction

Patients with squamous cell carcinoma of the hypopharynx (HPSCC) are often seen at an advanced stage and have a poor prognosis. The poor prognosis can be attributed to late presentation, aggressive local growth and submucosal spread, tendency toward lymphatic spread, and a high incidence of distant metastasis.

Patients with favourable T₁ or T₂ lesions can be treated with surgery or radiotherapy alone, and may have nearly normal swallowing and speech. Radical surgery followed by radiotherapy has been the standard therapy for patients with advanced stages HPSCC for several decades.¹ However, radical resection may result in loss of the larynx, which affects the quality of life. Recently, organ preservation protocols with a combination of chemotherapy and radiotherapy have been proposed to preserve the larynx,² although the survival was not significantly improved.

The authors reviewed the treatment results and failure patterns of HPSCC patients treated with combination of surgery and radiotherapy in their institute. The prognostic factors that predicted the

disease-specific survival (DSS) were analyzed. These results will also provide a background for comparing results from an organ preservation protocol that will be conducted in their institute in the near future.

Materials and methods

The authors reviewed the clinical records of 104 previous untreated patients who had surgery with or without post-operative radiotherapy in their institutes between January 1986 and December 1995. Their charts were reviewed for demographic data, sites of primary tumour, extent of local and regional disease, surgical procedures, reconstructive methods, post-operative complications, final pathologic finding, dosages of post-operative radiotherapy, site and date of recurrence and second primary tumour (SPT), status and date of last follow up.

Clinical and pathologic data were entered into a computer database (Microsoft® Access 2000), and statistical analysis was performed with a commercially available software package (JMP 4.0, SAS Institute Inc, Cary NC). The follow-up interval was calculated in months from the date of initial surgery

until death or the date of last follow up. For overall survival (OS), patients were counted as alive or dead, regardless of the causes. For DSS, patients who died of non-cancer related causes were censored at the date of death. Patients who died of SPT were censored at the date SPT occurred. OS, DSS, and tumour control rates were calculated by the Kaplan-Meier method and compared using the log-rank test. The level of statistical significance was selected at $p \leq 0.05$. All significant factors were entered into multivariate analysis using the Cox proportional hazard model.

Results and analysis

Of the 104 cases, there were 99 males and five females. Their ages ranged from 36 to 80 years, with a median of 61 years. The site of the primary main tumour was the pyriform sinus in 90 patients (87 per cent), posterior pharyngeal wall in seven (seven per cent), and postcricoid area in seven (seven per cent). The tumours were staged retrospectively according to the AJCC 1997 classification.³ Eighty-three patients (80 per cent) were at the advanced T₃ or T₄ stage, and 64 patients (62 per cent) had cervical lymph node metastasis. Eleven patients (11 per cent) were at stage II, 25 (24 per cent) at stage III, and 68 (65 per cent) at stage IV.

All patients received surgical resection of the primary tumour with, or without, neck dissection. While none had previous treatment for other head and neck cancers, five patients had neck biopsy and two had tracheostomy before definitive surgery. Conservation surgery with laryngeal preservation was performed in 13 patients (13 per cent), including endoscopic CO₂ laser excision in two and partial laryngopharyngectomy (PLP) in 11. Total laryngectomy (TL) was performed in 91 patients (87 per cent), including total laryngectomy with partial pharyngectomy in 68, total laryngectomy with total pharyngectomy in 12, and total laryngectomy with total pharyngoesophagectomy in 11. Neck dissection was performed in 98 patients (94 per cent), including ipsilateral neck dissection in 83 and bilateral neck dissection in 15.

Reconstructive methods for the surgical defect following total laryngectomy are shown in Table I. The pharyngeal defect was closed primarily in 14 patients (13 per cent). Pectoralis major myocutaneous flap (PMMCF) was used with either a tubed or

patch-on method in 36 patients (35 per cent). Since 1991, the technique of local laryngotracheal flap (LTF)⁴ or combination with PMMCF has become more popular in the reconstruction of pharyngeal defects in 38 patients (37 per cent). Gastric pull-up was used in 11 patients (11 per cent) with cervical oesophageal invasion. Only one patient had free jejunal flap reconstruction.

Post-operative complications are shown in Table II. Complications were classified as either early complications (during hospitalization) or late complications (after discharge). Forty-six patients (44 per cent) had complications post-operatively, including 31 (30 per cent) early complications and 26 (25 per cent) late complications. Eleven patients (11 per cent) had both early and late complications. The most common early local complication was pharyngocutaneous fistula in 15 patients (14 per cent). Nine patients (nine per cent) had wound infection, three had flap necrosis, and two had bleeding from the major vessels. Six patients had systemic complications, including chest infection in three, pleural effusion in two, and UGI bleeding in one. Eight patients had multiple early complications. The most common late complication was tracheostomal stenosis in 11 patients (11 per cent), and then pharyngoesophageal stenosis in 10 (10 per cent). Three patients had multiple late complications. The hospital mortality was three per cent (four of 104). Two patients died from blowout of the common carotid artery, and two patients died from severe chest infection.

The final pathological findings showed the size of primary tumour ranged from 12 to 80 mm (median 38 mm). The depth of tumour invasion ranged from three to 45 mm (median 15 mm). The grade of tumour revealed well-differentiated carcinoma in 21 patients (20 per cent), moderately differentiated carcinoma in 53 (51 per cent), poorly differentiated carcinoma in eight (eight per cent), and the grade was unknown in 22 (21 per cent). The status of surgical margins was available in 90 patients (87 per cent). Eighty-two patients (79 per cent) had negative

TABLE I

RECONSTRUCTIVE METHODS FOR THE SURGICAL DEFECT

Methods	No. (%)
Primary closure	14 (13)
Laryngotracheal flap	29 (28)
Laryngotracheal flap and patch-on PMMCF	9 (9)
PMMCF (only)	36 (35)
-Tubed method	11 (11)
-Patch-on method	25 (24)
Gastric pull-up	11 (11)
Free jejunal flap	1 (1)
Stenocleidomastoid muscular flap	2 (2)

TABLE II
POST-OPERATIVE COMPLICATIONS

Complications	No. (%)
Early complications	31 (30)*
<i>Local</i>	
Pharyngocutaneous fistula	15 (14)
Wound infection	9 (9)
Flap necrosis	3 (3)
Bleeding	2 (2)
Others	5 (5)
<i>Systemic</i>	
Chest infection	3 (3)
Pleural effusion	2 (2)
UGI bleeding	1 (1)
Late complications	26 (25)*
Tracheostomal stenosis	11 (11)
Pharyngoesophageal stenosis	10 (10)
Hypothyroidism	7 (7)
Soft tissue necrosis	1 (1)
Perioperative mortality	4 (3)

*Some patients had multiple complications

margins and eight (eight per cent) had positive margins. The final pathologic tumour stage was T₂ in 20 patients (19 per cent), T₃ in 28 (27 per cent), and T₄ in 56 (54 per cent). Cervical lymph node metastasis was confirmed in 72 patients (69 per cent). In the 40 clinical N₀ necks undergoing elective neck dissection, 16 (40 per cent) had occult metastasis. In the 64 clinical N₊ necks, 56 (88 per cent) had pathologically confirmed metastasis. The final pathologic overall stage was stage II in eight patients (eight per cent), stage III in 19 (18 per cent), and stage IV in 77 (74 per cent).

Sixty-nine patients (66 per cent) received radiotherapy, including two planned pre-operative radiotherapy treatments and 67 post-operative radiotherapy. The criteria for post-operative radiotherapy included pathological T₄ tumour, advanced N₂ or N₃ neck, and unfavourable pathologic features (such as positive surgical margins, perineural invasion, lymphovascular invasion, or extracapsular nodal extension). The median radiation dose was 6000 cGy (ranged 4000 to 7400 cGy) to the primary site and 6000 cGy (range 3000 to 7400 cGy) to the neck. Only three patients received a radiation dose less than 5000 cGy.

With a median follow-up of 50 months (range from one to 182 months), the five-year OS and DSS were 47 per cent and 62 per cent (Figure 1). The five-year local, regional, and local-regional control rates were 86 per cent, 76 per cent and 69 per cent, respectively. For DSS according to the tumour stage, the five-year survival rates were T₂, 78 per cent; T₃, 61 per cent; T₄, 64 per cent. For the DSS according to the nodal stage, the five-year survival rates were N₀, 78 per cent; N₁, 71 per cent; N₂, 56 per cent; N₃, 100 per cent (only one patient). For the DSS according to the overall stage, the five-year survival rates were stage II, 88 per cent; stage III, 72 per cent; stage IV, 61 per cent. The prognostic factors affecting the DSS are listed in Table III. Four patients were excluded from this analysis because of hospital mortality. In univariate analysis, the site and size of primary tumour, neck biopsy before surgery, early post-operative complications, and pathological nodal stage (multiple nodal metastasis) were significant prognostic factors. The neck biopsy before surgery and site of primary tumour were independent factors in multivariate analysis.

The failure patterns are shown in Figure 2. Thirty-eight patients (37 per cent) developed recurrence, including 12 (12 per cent) with local recurrence, 22 (21 per cent) with regional recurrence, and 12 (12 per cent) with distant metastasis. Sixteen patients had recurrence at multiple sites. The time of recurrence occurred ranged from two to 39 months (median 11 months), 34 of the 38 patients (89 per cent) occurred within two years. In the 38 patients with recurrence, 16 patients (42 per cent) had salvaged treatment but only seven patients (18 per cent) had successful salvage. In the 12 patients with local recurrence, 10 had post-operative radiotherapy. Seven of the 91 patients undergoing total laryngectomy (eight per cent) had local recurrence and five of

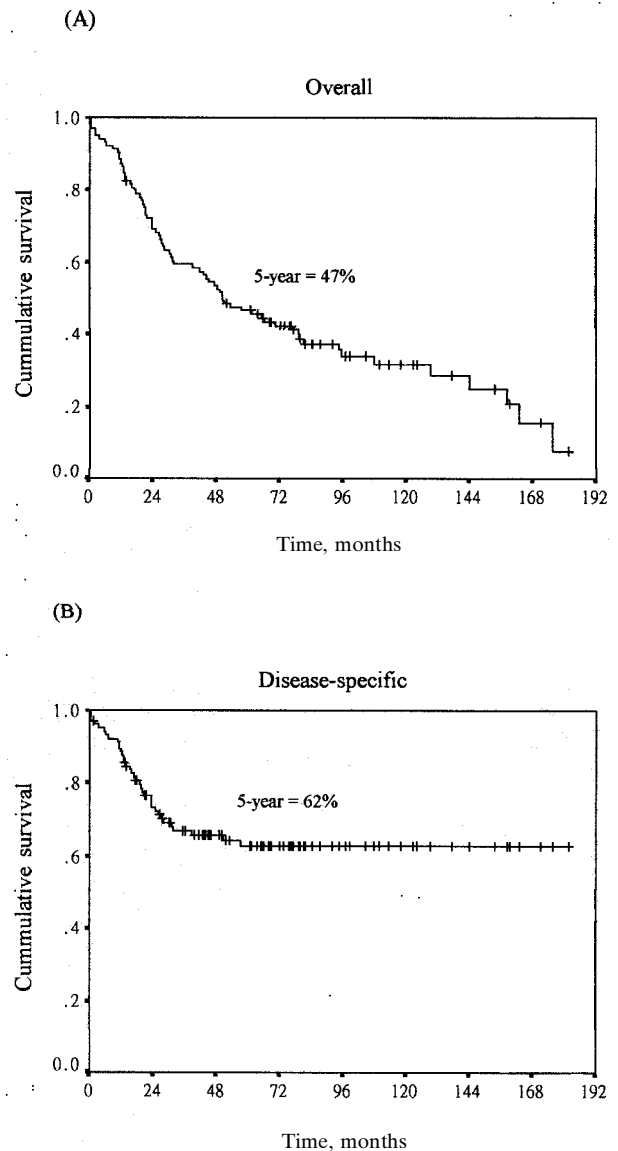


FIG. 1

Overall survival (A) and disease-specific survival (B).

13 patients undergoing conservation surgery had local recurrence (38 per cent). Patients with conservation surgery had a higher local recurrence rate than the total laryngectomies (Fisher's Exact test, $p = 0.006$). Three of the 12 patients with local recurrence had positive surgical margins, seven had negative margins, and two had unknown margin status. Patients with positive surgical margins had a higher local recurrence rate than negative margins (38 per cent vs. nine per cent; Fisher's Exact test, $p = 0.047$). In the 22 patients with regional recurrence, 12 occurred in the ipsilateral neck, nine in the contralateral neck, and one in the bilateral neck. Of the 12 patients with ipsilateral neck recurrence, 11 had undergone neck dissection and six had radiotherapy post-operatively. Nine of the patients (75 per cent) had pathological N₂ neck. Four of the five patients with neck biopsy before definitive surgery had ipsilateral neck recurrence. Of the nine patients

TABLE III
PROGNOSTIC FACTORS FOR DISEASE-SPECIFIC SURVIVAL

Factors	No.	5-year survival	<i>p</i> -value (LR test) [†]	<i>p</i> -value (Cox test) [‡]
Site of primary tumour				
Pyriform sinus	86	67%		
Postcricoid area	7	86%	0.008	0.028
Posterior pharyngeal wall	7	29%		
Neck biopsy before surgery				
No	95	68%	0.005	0.025
Yes	5	20%		
Early post-operative complications				
Yes	27	37%	0.0003	0.053
No	73	76%		
Size of primary tumour*				
<40 mm	41	82%	0.028	0.079
≥40 mm	40	56%		
Pathologic nodal stage				
N ₀ or single node	52	76%	0.021	0.286
Multiple nodes	48	53%		

[†]Log rank test; [‡]Cox proportional hazard model; *data unavailable in some patients

with contralateral neck recurrence, all had ipsilateral neck dissection and none had contralateral neck dissection, although five of them had radiotherapy post-operatively. Seven of the nine patients with contralateral neck recurrence had tumour extension across the midline of the postcricoid area or posterior pharyngeal wall. In the 12 patients with distant metastases, in nine patients it occurred in a solitary organ, including six in the lung, two in bone, one in the liver. Three patients had metastases occurring at multiple sites, all of whom had lung metastasis. Ten of the 12 patients (83 per cent) had cervical lymph node metastasis. The median time to develop distant metastases from initial treatment was 14 months, ranging from six to 33 months. The median survival from the initial diagnosis of distant metastasis was four months and the five-year survival was eight per cent.

Twenty patients (19 per cent) developed SPT during the follow-up period. The time of SPT occurrence ranged from four to 132 months (median 48 months). The SPT included oesophagus in seven patients, oropharynx in five, liver in three, oral cavity in two, lung in two, and paranasal sinus in one. In eight of the 20 patients (40 per cent) the SPT occurred in the head and neck regions and in 12 (60 per cent) it occurred in the non-head and neck regions.

Discussion

Since the majority of patients with HPSSC have it at an advanced stage, combination therapy with surgery and post-operative radiotherapy has been the standard treatment for several decades. Although combination of chemotherapy and radiotherapy for the purpose of organ preservation has become popular in recent years, surgical treatment still plays an important role primary treatment, especially for advanced T₄ cancers with extensive cartilage destruction and in patients who require pretreatment tracheotomy.⁵ In the authors' institute, an organ preservation protocol has been used for selected HPSSC patients since 1996. Combination surgery and radiotherapy was the main treatment for most patients before this period. Treatment results' data and failure patterns of this cohort are also important in providing a background for comparing results from organ preservation protocol in the near future.

Because of the submucosal extension of the HPSSC, radical excision with total laryngectomy and partial or total pharyngectomy is often considered for more patients to acquire adequate surgical margins. In a review of the literature, only 15 to 34 per cent of the HPSSC patients treated with surgery were found to be suitable for larynx-sparing surgery.^{1,6,7} In this study, only 13 patients (13 per cent) were suitable for conservation surgery of the larynx. The reasons for the low percentage of larynx-sparing surgery performed may be due to the more advanced tumour stage in this series (80 per cent of the patients with T₃ or T₄ tumour).

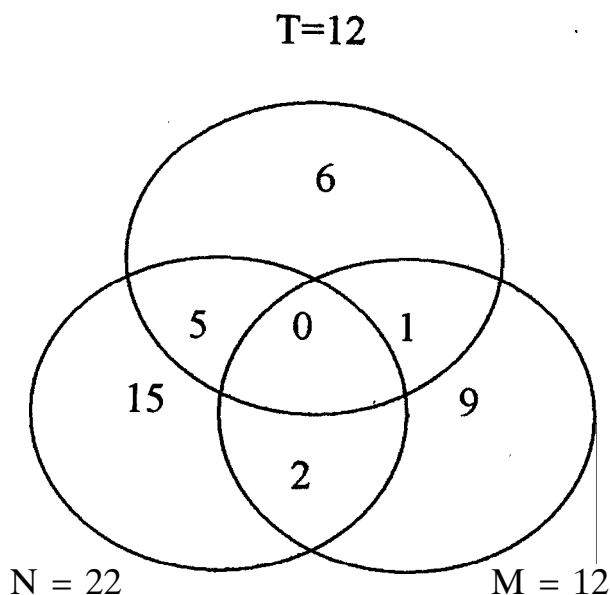


FIG. 2

Failure patterns of the patients (T = tumour; N = node; M = distant metastasis).

Neck dissection is an essential part of the surgical treatment of HPSCC. The reported incidence of neck metastasis of HPSCC was from 65 to 80 per cent,^{8–11} and 30 to 40 per cent^{8,9} of N₀ necks were subsequently found to have histological evidence of metastasis following elective neck dissection. In this study, 69 per cent of the patients had pathologic cervical lymph node metastasis and 40 per cent of the patients had occult cervical metastasis. Because of the high incidence of occult cervical metastasis, elective neck dissection is recommended for all the patients with a clinical N₀ neck.

Radical surgery usually results in a large or even circumferential defect of the pharyngeal or pharyngo-oesophageal segment. Restoration of the alimentary continuity after major ablation procedures is critical and challenging for maintaining a good quality of life. The authors used the following methods of reconstruction at their institute: (1) if the pharyngeal defect could not be closed with a primary closure, then the contralateral unaffected LTF is used for pharyngeal closure; (2) a circumferential defect of pharynx is reconstructed with the LTF and a patch-on PMMCF flap; however, if the LTF appears oncologically unsafe, then a free fasciocutaneous or jejunal flap is considered; (3) in cases when the tumour had invaded the cervical oesophagus, gastric pull-up was used to reconstruct the pharyngo-oesophageal defect. A free jejunal flap was used uncommonly in the authors' department, because of the morbidity of the donor site and the patient's intention. The local LTF has been proved to be a simple and less time-consuming method with high applicability and good oncological results.^{4,12} It also reduces the chance of other regional pedicle flaps or free flaps used.

In the literature, the reported five-year survival rate ranged from 25 per cent to 60 per cent in patients with HPSCC who had surgery with, or without, post-operative radiotherapy.^{1,6,7,13–15} In this series, the five-year OS and DSS were 47 and 62 per cent, respectively. The survival declined as a function of a more advanced overall stage. The five-year DSS by overall stage was as follows: stage II, 88 per cent; stage III, 72 per cent; and stage IV, 61 per cent. Although a more advanced overall stage had a poor prognosis, there was no statistical significance among the overall stage. The five-year DSS also showed a decline with nodal disease as follows: N₀, 76 per cent; N₁, 71 per cent; N₂, 57 per cent (when the authors excluded the only one patient who had N₃ neck and was alive more than five years). The survival was not statistically significant with nodal diseases. The five-year DSS also showed no statistical significance with tumour stage (T₂, 78 per cent; T₃, 78 per cent; T₃, 61 per cent; T₄, 64 per cent). The survival revealed almost the same between T₃ and T₄ stage. The surgical treatment has achieved a good local-regional control in this study. It provided the best chance for local-regional control and palliation for dysphagia and airway problems. There is no reason to abandon surgery as the treatment option for hypopharyngeal cancer patients.

- **104 patients with advanced squamous cell carcinoma of the hypopharynx who had undergone primary surgery were analysed**
- **The authors concluded that surgery with, or without, post-operative radiotherapy has achieved good local-regional control and survival**
- **Regional recurrence was the most common site of treatment failure**
- **Bilateral neck dissection for cases with tumour spread across the midline and the avoidance of neck node biopsy before surgery may reduce regional recurrence**

Analysis of clinicopathologic factors affecting the DSS, the site of primary tumour shown was statistically significant in both univariate and multivariate analysis. Tumours in the posterior pharyngeal wall had a poorer prognosis than in the pyriform sinus and postcricoid area (29 per cent vs. 67 per cent, 86 per cent). The poor prognosis may be due to extensive invasion of primary tumour and high incidence of bilateral neck metastasis. Three of the seven patients with posterior pharyngeal wall tumour had cervical oesophageal invasion and three of them had bilateral neck metastasis. However, the site of primary tumour did not show any significant difference in Kraus *et al.*'s report.⁶ The five-year DSS was 44 per cent in patients with posterior pharyngeal wall tumour and 41 per cent in pyriform sinus tumour in their study. Although only five patients had neck biopsy before definitive surgery, patients with neck biopsy had a poorer five-year DSS than those without neck biopsy (20 per cent vs. 68 per cent). Four of the five patients with neck biopsy had ipsilateral neck recurrence during follow-up, although post-operative RT was given in all of them. It has been reported that node biopsy before definitive treatment of cervical metastatic carcinoma may increase wound necrosis, local cervical recurrence, distant metastasis, and decrease the chance for survival.¹⁶

Patients with early post-operative complications had poorer prognosis than those without complications (37 per cent vs. 76 per cent), which was statistically significant by univariate analysis and showed borderline significance by multivariate analysis. The reasons of poor prognosis may be due to post-operative complications delaying adjuvant therapy after surgery. A meta-analysis showed that delay in initiating radiotherapy had an adverse effect on local-regional control in head and neck cancer, and the authors recommend that delays in initiating radiotherapy should be as short as possible.¹⁷ Although the primary tumour and nodal stage were not significant by multivariate analysis, larger primary tumours (≥ 4 cm) and multiple cervical lymph node metastases had poor prognosis by

univariate analysis. More detailed classification of the tumour and nodal stage may have good correlation with survival.

Recurrence of the tumour occurred in 37 per cent of the patients in this series. The failure patterns showed the neck was the most common site of recurrence and then local and distant sites. The reported local recurrence rate ranged from four per cent to 20 per cent of the HPSCC patients with surgical treatment,^{1,6,11,15} as compared to 12 per cent in this study. Kraus *et al.*⁶ reported an 18 per cent incidence of local recurrence with combination surgery and radiotherapy for HPSCC, which occurred in a similar proportion in patients with negative and positive margins. The authors' result was different from their report that patients with positive margins had a higher local recurrence rate than those with negative margins (38 per cent vs. nine per cent, $p = 0.047$). However, the five-year DSS did not show any significant difference between these two groups (63 per cent vs. 67 per cent, $p = 0.482$). The authors' data also showed that patients with conservation surgery had a higher local recurrence rate than patients with total laryngectomy (36 per cent vs. eight per cent, $p = 0.0098$). The reason may be due to the fact that only limited surgical margins can be achieved during conservation surgery in order to preserve laryngeal functions. Therefore, when conservation surgery is considered for the treatment of HPSCC, patients should be selected carefully.

Regional recurrence (21 per cent) was the most common site of treatment failure in this series. In the patients of ipsilateral neck recurrence, 75 per cent of them had advanced nodal diseases (N₂, N₃), although neck dissection and post-operative RT was given. Almost half of the recurrence occurred in the contralateral or bilateral necks. All of the patients with contralateral neck recurrence had only received ipsilateral neck dissection and more than half of them (five out of nine) had received post-operative radiotherapy. Careful evaluation of the tumour extension and bilateral neck dissection in the patients with tumour across the midline may reduce the contralateral neck recurrence. Johnson *et al.*¹¹ also recommended bilateral neck dissection for patients with carcinoma of the medial wall of the pyriform sinus because these patients were at risk for contralateral cervical metastasis in their study.

As local and regional control of head and neck cancer has improved, distant metastases have become an increasingly common cause of death. Distant metastasis occurred in 12 per cent of the authors' patients, which was consistent with previous reports of four per cent to 25 per cent.^{18–20} The lung was the most common site of distant metastasis, and bone and liver were the only other sites. Patients with more extensive neck disease developed distant metastasis more frequently. The prognosis was poor and the median survival time was usually less than one year.

The incidence of SPT in head and neck cancers has been reported to be between 10 and 40 per cent,²¹ and the SPT is the major cause of death in patients who present with early stage disease. In this series, the tumour's recurrence usually occurred within the first three years and the SPT developed in later years after treatment (median four years). The incidence of SPT was 19 per cent and 70 per cent of them (14/20) developed in the upper digestive tract. The high incidence of SPT in the upper digestive tract can be explained by the theory of field cancerization proposed by Slaughter *et al.*²² However, it should be carefully differentiated from local recurrence of the primary tumour, because of the possibility of submucosal extension.

Regular follow up and early diagnosis of the SPT are essential, although the therapeutic modalities are often limited because of prior surgery and the cumulative radiation dose. The authors have developed a technique of videofibre-optic examination of pharyngoesophageal segment in patients after total laryngectomy.²³ It enables early diagnosis of local recurrence and SPT in the upper digestive tract. Furthermore, recent development of chemoprevention with retinoids appears effective in preventing SPT, although it did not prevent recurrences of the original tumour.²⁴

Conclusions

Surgery with, or without, post-operative radiotherapy in the treatment of patients with HPSCC has achieved good local-regional control and survival. Regional recurrence is the most common site of treatment failure. Bilateral neck dissection for the tumour across midline and avoiding neck node biopsy before surgery may reduce regional recurrence.

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