

Evaluation of a new diagnostic modality for distal assessment of advanced, obstructing hypopharyngeal cancer

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Abstract

Introduction: Pre-operative endoscopic assessment of the distal extension of hypopharyngeal cancer is essential for proper surgical extirpation. This assessment is frequently not feasible in advanced, obstructing tumours.

Aims: To study the role of a proposed new diagnostic technique: intra-operative open oesophagoscopy, in distal assessment of advanced hypopharyngeal cancer.

Materials and methods: A clinicopathological study, including 35 consecutive patients with obstructing hypopharyngeal cancer.

Results: Intra-operative open oesophagoscopy revealed inferior submucosal tumour extension in 19 out of 22 cases proven histopathologically, with a sensitivity, specificity and accuracy of 86, 100 and 91 per cent, respectively. Oesophageal skip lesions were detected in two cases. Intra-operative open oesophagoscopy findings surpassed data obtained from pre-operative radiological investigations and influenced the extent of resection performed. Accordingly, 19 patients had a total laryngopharyngectomy for local disease control, while 16 patients needed an additional total oesophagectomy. Histopathologically negative inferior resection margins were obtained in all cases.

Conclusions: Intra-operative open oesophagoscopy was found to be a reliable diagnostic modality for distal assessment of obstructing hypopharyngeal cancer in cases in which pre-operative distal endoscopic examination was not feasible.

Key words: Hypopharyngeal Neoplasms; Neoplasm Staging; Oesophagus; Endoscopy

Introduction

Hypopharyngeal cancer is considered to be one of the deadliest of the squamous cancers arising in the upper aerodigestive tract. The difficulty in managing this cancer lies in the fact that it usually presents late and at an advanced stage.¹

Accurate pre-operative assessment of the hypopharyngeal tumour inferior limit, as well as of the condition of the oesophagus distal to the tumour, greatly influences the extent of resection required and, hence, the type of reconstruction that is to be employed.² However, in advanced hypopharyngeal cancer with near-total or total obstruction of the upper oesophageal lumen, this assessment may be difficult and frequently impossible when using routine radiological and endoscopic methods.^{3,4}

In this article, we describe and evaluate a new diagnostic modality that allows accurate distal assessment of advanced, obstructing hypopharyngeal cancer – intra-operative open oesophagoscopy (IOOO). This is performed before commencing the

resection, which can then be tailored according to the magnitude of distal disease found.

Materials and methods

Patient data

From January 2001 to December 2004, 61 patients underwent surgical resection for hypopharyngeal cancer in the department of otolaryngology – head and neck surgery, Alexandria Main University Hospital, Alexandria, Egypt. This study was carried out on 35 of these 61 patients (57 per cent), in whom pre-operative endoscopy failed to evaluate the hypopharyngeal tumour lower limit as well as the condition of the entire oesophageal lumen, due to significant luminal obstruction. Patients comprised 22 men and 13 women (male/female ratio 1.7:1) ranging in age from 26 to 70 years, with a mean age of 48 years.

It was difficult to identify the precise origin of the primary tumour in most of the cases due to

considerable encroachment on more than one subregion of the hypopharynx. The incidence of tumour involvement was 91, 80 and 43 per cent for the piriform fossa, postcricoid area and posterior pharyngeal wall, respectively.

All patients had surgical resections in the form of a total laryngopharyngectomy (TLP) with or without a total oesophagectomy, according to tumour extent. Appropriate neck dissections were carried out to control neck disease. Reconstruction was performed by either a microvascular free flap (jejunum or tubed radial forearm flap) for circumferential pharyngoesophageal defects limited to the neck or by gastric pull-up for those patients requiring a total laryngopharyngoesophagectomy (TLPO).

Thirty-one patients (89 per cent) did not receive any previous treatment. Only four patients (11 per cent) had received previous radiotherapy. Post-operative radiotherapy and/or chemotherapy was given to 26 patients who survived the operation.

Pre-operative evaluation

All patients underwent a recent barium swallow X-ray and a computed tomography (CT) neck and chest scan within one week of the operation. The lower border of the cricoid cartilage was taken as a fixed anatomical landmark. The distance between this point and the lower tumour margin, as seen in the barium swallow and CT, was measured and compared with the same gross measurement on the excised specimen.

Tumour dimensions were calculated on the lateral view barium swallow films by measuring the distance from the level of the lower border of the cricoid cartilage (identified in relation to cervical vertebrae on plain X-ray films) down to the lower tumour margin (denoted by normal barium reflux). The magnification factor in barium swallow films was taken into consideration. This factor was measured by calculating the difference between a measure on a radio-opaque ruler and the same measure on the same ruler in barium films (Figure 1).

Measures from CT scans were calculated by subtracting the difference in table position between the lower border of the cricoid cartilage and the suspected lower tumour margin.

By the criterion of selection, although all patients had undergone a pre-operative panendoscopic assessment under general anaesthesia, this had failed to assess the lower tumour limit due to tumour bulk obstruction.

Intra-operative open oesophagoscopy

Open oesophagoscopy was performed intra-operatively just before tumour resection and after ensuring tumour resectability (by excluding prevertebral fascia or musculature and carotid artery involvement). The gutter between the sternocleidomastoid muscle and the visceral compartment of the neck was opened to identify the upper part of the oesophagus in the lower neck. The lower limit of the obstructing tumour mass was determined by palpation, and a tumour-free segment of the cervical



FIG. 1

Barium swallow study, lateral view, of an advanced hypopharyngeal tumour. Note radio-opaque ruler used for calibration.

oesophagus was selected. A small, 1–1.5 cm incision was made in this segment, large enough to allow introduction of a size 6 paediatric oesophagoscope (Karl Storz, Tuttlingen, Germany) (Figure 2). The examination was performed using a Hopkins® telescope 0° (Karl Storz) introduced through the oesophagus, up to the cardioesophageal junction, was then routinely examined to adequately assess the inferior tumour limit as well as the condition of the oesophagus distal to the main obstructing tumour, thereby detecting any oesophageal skip lesions or second primaries. Inferior submucosal spread was suspected on observation of thickening, congestion, minor ulceration or induration of the mucosa inferior to the tumour's macroscopic inferior limit. The extent of suspected inferior submucosal spread was measured and reported.

Pathological study

All resected specimens were opened at the posterior midline and examined immediately after resection. The specimen was photographed and the macroscopic appearance of the tumour, as well as any submucosal tumour extension, was recorded. The

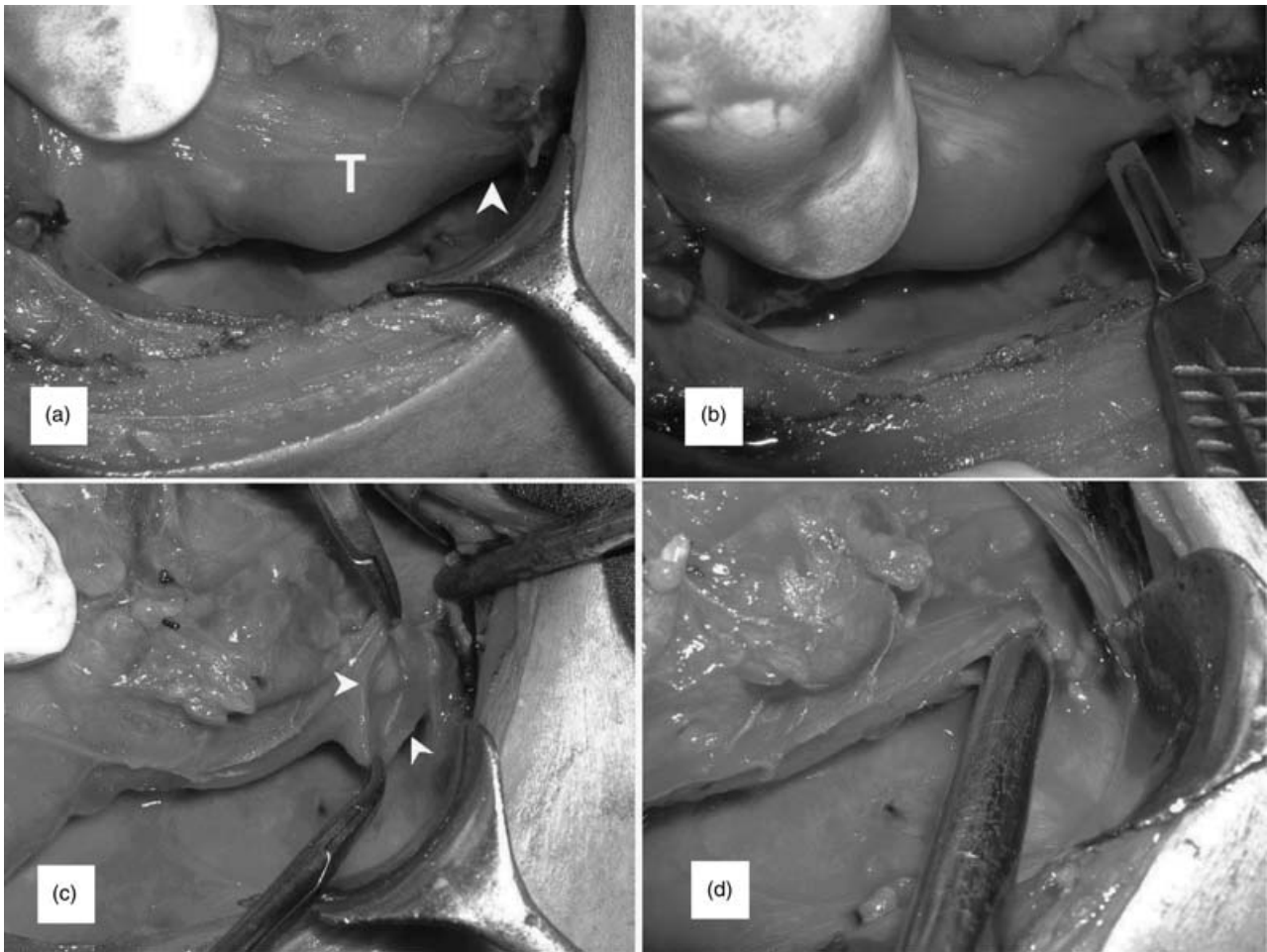


FIG. 2

Steps of intra-operative open oesophagoscopy. (a) Identification of cervical oesophagus (arrowhead) below palpable lower end of tumour (T). (b) Incision (about 1 cm long) made in selected segment of cervical oesophagus. (c) Oesophagotomy completed; arrowheads mark its edges. (d) Paediatric oesophagoscope introduced via the oesophagotomy for distal assessment.

distance between the lower border of the cricoid cartilage and the gross lower tumour edge was measured (Figure 3) and compared with the same measurements obtained from the pre-operative barium swallow and CT scan studies. The whole specimen was then immersed in 10 per cent buffered formalin solution.

After adequate formalin fixation and decalcification using 1 per cent formic acid, the specimen was cut transversely into sections (3 to 5 mm thick) using a slicing machine. For the patients who had undergone a TLPO, the oesophagus was sectioned at 3 to 5 mm intervals, up to 5 cm from the inferior tumour edge; then the rest of the oesophagus was sectioned at 1 cm intervals. The sections were routinely processed, stained with haematoxylin and eosin and examined under light microscopy to detect the extent of inferior submucosal spread as well as the distal oesophageal tumour involvement.

Results and analysis

Statistical analysis

All collected data were entered into an IBM-compatible computer database using Microsoft®

Excel 2003 software (Microsoft Corporation). Data analysis was performed using the commercially available statistical package for the social sciences (SPSS) software version 11.5 (SPSS Inc, Chicago, Illinois, USA). Descriptive statistics were reported in the form of proportion, mean and/or median whenever appropriate. Measures of accuracy such as sensitivity and specificity were calculated. Measures of agreement were calculated using the Kappa test. Groups were compared by use of the chi-squared test. Outcome analysis was computed using the Kaplan–Meier method and comparisons were made using the log-rank test. A statistically significant difference was reached at $p \leq 0.05$.

Pre-operative investigations

The barium swallow studies gave more identical results than did the CT scans (32 vs 23 per cent) in assessing the macroscopic lower tumour limit when compared to the actual gross measurements obtained from the operative specimens (Table I). However, this difference failed to reach statistical significance ($\chi^2 = 0.65$, $p = 0.42$). There was a general tendency for barium studies to underestimate and for CT to

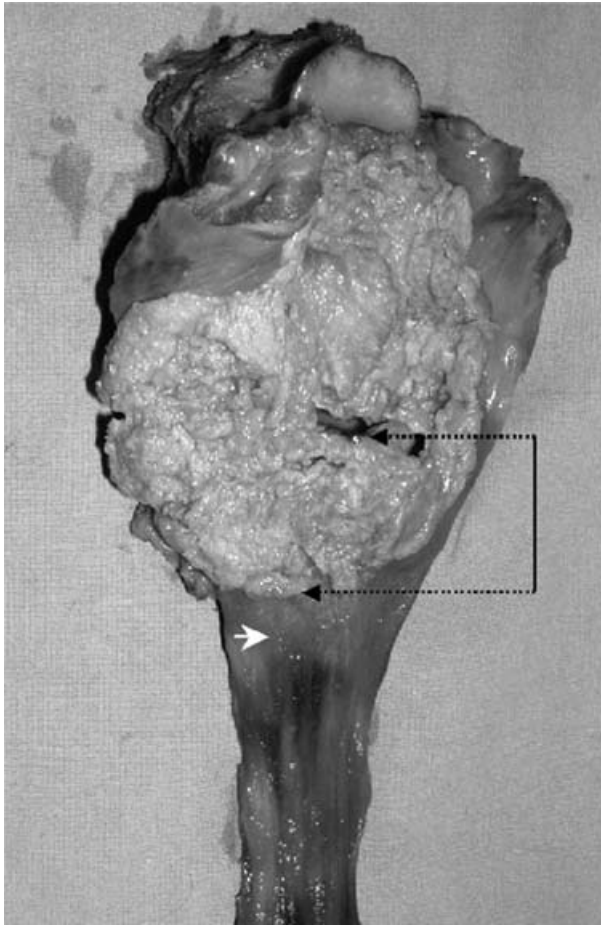


FIG. 3

Total laryngopharyngoesophagectomy specimen, opened along the posterior midline, showing the measured distance from a pin inserted at the lower border of the cricoid cartilage to the gross lower tumour edge (black arrows) and the inferior submucosal tumour extension (white arrow).

overestimate the lower extent of the hypopharyngeal tumour. Both barium and CT studies were unable to accurately assess submucosal spread inferior to the gross lower tumour margin and were unable to detect oesophageal skip lesions.

Operative and pathological findings

The hypopharyngeal tumour inferior limit was assessed using the IOOO technique described above and the results compared with those obtained from histopathological whole-organ serial sections of

TABLE I

ACCURACY OF PRE-OPERATIVE RADIOLOGICAL INVESTIGATIONS IN ASSESSING MACROSCOPIC LOWER LIMIT OF HYPOPHARYNGEAL CANCERS*

Investigation	Identical [n (%)]	Underestimated [n (%)]	Overestimated [n (%)]
Barium swallow	11 (32)	19 (54)	5 (14)
CT scan	8 (23)	9 (26)	18 (51)

*In 35 patients, compared with resected operative specimens. CT = computed tomography

the resected specimen. Inferior submucosal spread was found histopathologically in 22 (63 per cent) out of the 35 examined specimens. Accordingly, four groups of cases were recognized, as follows.

Group 1. This group was characterized by submucosal extension, evident during IOOO as marked induration with mucosal elevation below the macroscopic lower edge of the tumour. This was found in 17 cases (49 per cent) and the length of the affected area ranged from 10 to 24 mm (mean, 17.1 ± 4.1 mm). Whole-organ serial sections of the corresponding specimens proved the presence of submucosal spread inferiorly in all these cases, with lengths ranging from 13 to 28 mm (mean, 19 ± 4.8 mm).

Group 2. This group was characterized by skip lesions, in which the submucosal tumour was separated from the primary tumour by a bridge of normal mucosa. Intra-operative open oesophagoscopy diagnosed skip lesions in two cases (6 per cent), in which lesions appeared as small, grossly distinct satellite nodules covered by intact healthy mucosa, scattered along the length of the oesophagus (Figure 4). This finding was confirmed by studying the serial sections of the resected specimens.

Group 3. In this group (three cases, 9 per cent), no signs of inferior submucosal extension were detected by IOOO, although submucosal spread was detected histopathologically. The length of submucosal spread in these cases was 4, 7 and 10 mm.

Group 4. In this group (13 cases, 37 per cent), no submucosal spread was detected by either IOOO or histopathological analysis.

According to these findings, the sensitivity, specificity and accuracy of IOOO in detection of inferior submucosal tumour extension was 86, 100 and 91 per cent, respectively. By use of the Kappa test, there was a significant agreement between IOOO and histopathological serial sectioning in the detection of inferior submucosal spread (Kappa = 0.825, $p = 0.00$).

The extent of resection required for control of the primary hypopharyngeal cancer was determined by the data obtained from the IOOO. The thoracic oesophagus was preserved only after ensuring that its entire length was free of tumour and that the inferior resection margin would leave an oesophageal stump long enough to permit a safe anastomosis to the transferred free flap within the neck. Accordingly, 19 patients (54 per cent) received a TLP with an inferior margin of at least 2 cm of normal looking mucosa included in the resection, thereby creating a circumferential pharyngoesophageal defect limited to the neck (Figure 5). None of these inferior resection margins proved positive on histopathology. Thirteen of the TLP defects were reconstructed using a tubed radial forearm free flap, while the other six defects were reconstructed using a free jejunal autograft.

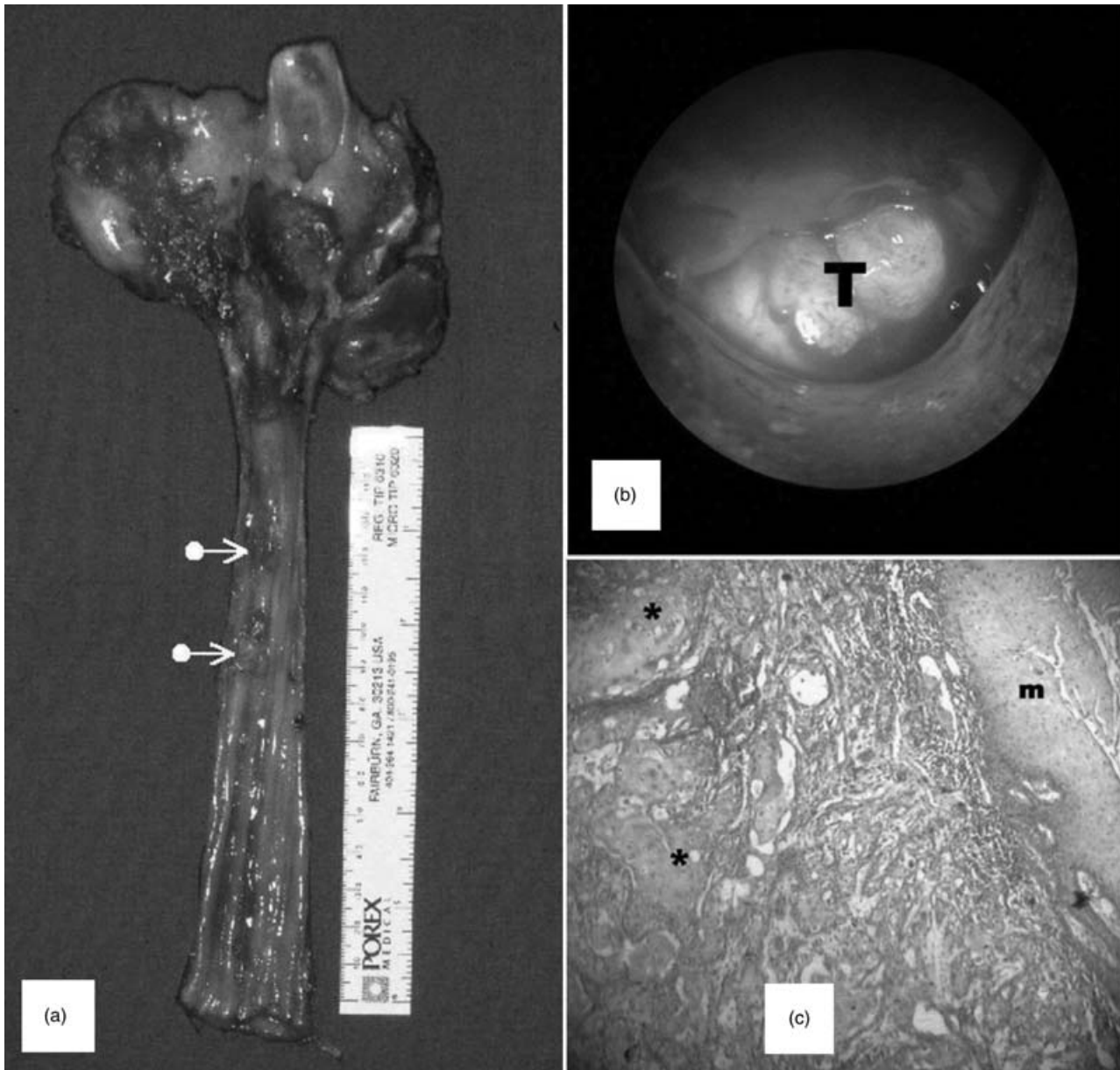


FIG. 4

Oesophageal skip lesions. (a) Total laryngopharyngoesophagectomy specimen, opened posteriorly, showing multiple oesophageal skip lesions (white arrows) separated from primary hypopharyngeal tumour. (b) Intra-operative open oesophagoscopy view of the same case, identifying skip lesions as distinct satellite nodules (T) covered by intact mucosa. (c) Histopathological examination of a nodule, showing intact mucosa (m) with submucosal malignant infiltration (*) (H&E; $\times 100$).

The inferior extent of the tumour and/or presence of disease in the distal thoracic oesophagus, proven during IOOO, mandated a TLPO in the remaining 16 patients (46 per cent); these patients' defects were reconstructed using a gastric pull-up procedure.

Clinical outcome

Two patients died in hospital before discharge. Both had undergone a TLPO resection and received a gastric-pull up reconstruction, thus giving this procedure a peri-operative mortality rate of 12.5 per cent (2/16). Cardiovascular instability and necrosis of the stomach were the causes of death, at seven and 13 days after the operation, respectively. All

free flaps survived well, with only one case of jejunum autograft requiring revision of its venous anastomosis.

The 33 patients surviving the operation were followed up for periods ranging between six and 52 months (mean follow up, 19 ± 13.8 months; median follow up, 14 months). The clinical results regarding tumour recurrence and overall patient outcome for these 33 patients are given in Table II. Analysis of data using the Kaplan–Meier method and comparisons using the log-rank test showed that neither survival ($p = 0.76$) nor incidence of loco-regional recurrence ($p = 0.60$) differed significantly between patients receiving a TLP compared with those receiving a TLPO.

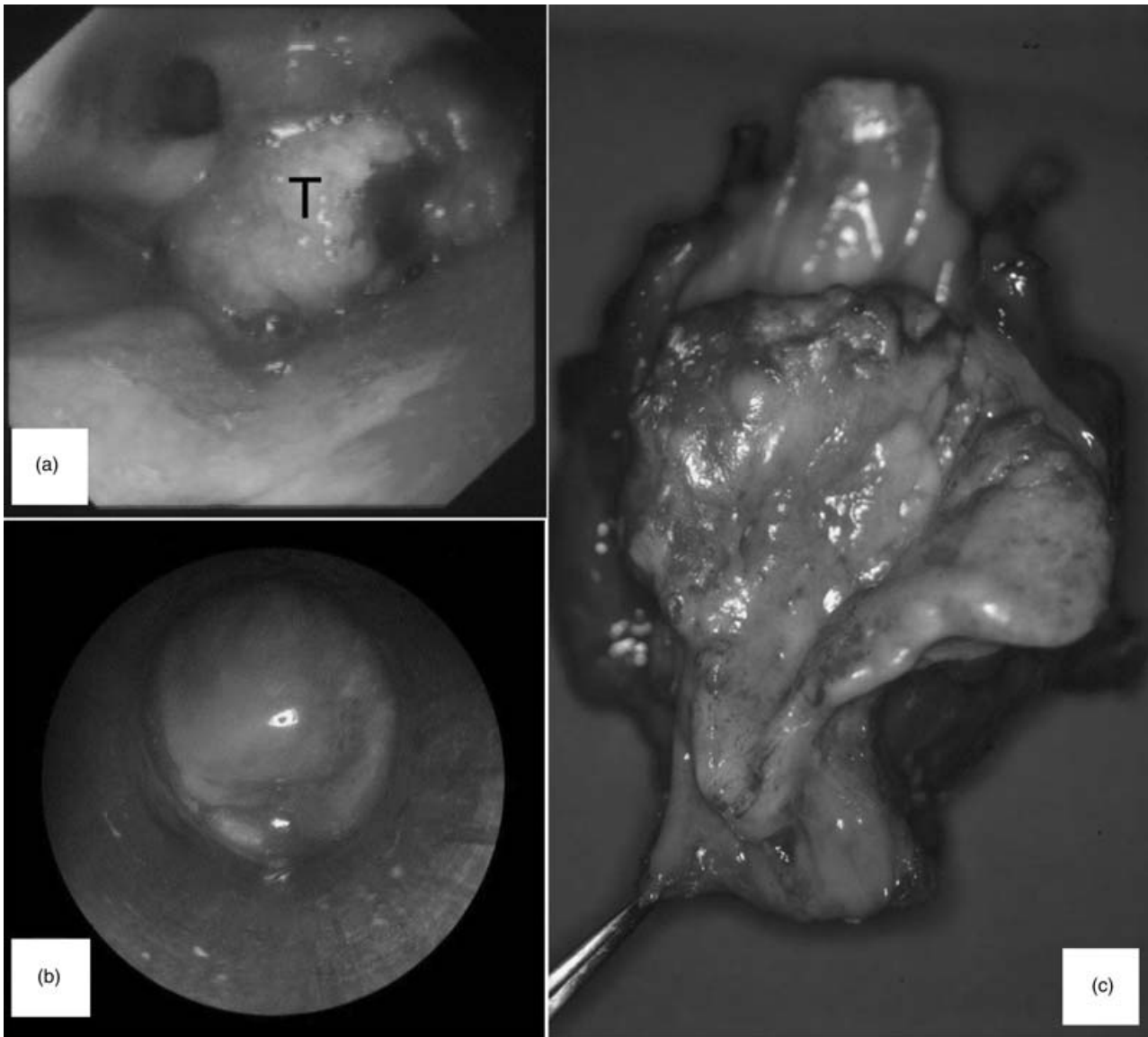


FIG. 5

(a) Pre-operative endoscopic view showing the top end of an obstructing hypopharyngeal cancer (T). Endoscopic distal assessment was not possible pre-operatively. (b) Intra-operative open oesophagoscopy demonstrated free distal oesophageal mucosa. (c) Total laryngopharyngectomy specimen of same patient, opened posteriorly to demonstrate the bulky, obstructing nature of the tumour.

Discussion

Of all the head and neck cancers, hypopharyngeal carcinoma has been considered one of the most challenging to manage. This aggressive disease has a tendency to present late, with a high propensity towards early cervical lymph node metastasis and extensive submucosal tumour spread.⁵ For the majority of advanced hypopharyngeal carcinomas, radical resection of the primary tumour plus neck dissection, followed by post-operative radiotherapy, offers a good chance of eradicating the disease.⁶

The ultimate goal of surgery is to resect tumour tissue in order to effect an adequate curative resection while removing as little normal tissue as possible, aiming to reduce mortality and morbidity. This optimal balance can only be achieved when the surgeon appreciates the exact extensions of the tumour.

Accurate assessment of the lower end of the hypopharyngeal tumour is of particular importance, as it greatly influences not only the amount of tissue that needs to be resected but also the reconstruction options (which may be completely changed). Pre-operative endoscopic examination under general anaesthesia remains the most definitive method of performing this assessment.⁷ However, in advanced hypopharyngeal cancer with considerable obstruction of the pharyngoesophageal lumen, whilst it is easy to see the top end of the tumour, it is often difficult (and frequently impossible) to pass an oesophagoscope through the tumour to assess its lower limit.

Several authors^{3,4,8} have reported difficulties in assessing the lower limits of obstructing hypopharyngeal tumours and have proposed different solutions. One such suggestion is to dilate the tumour with bougies, leaving a filiform bougie in the oesophageal

TABLE II
PERI-OPERATIVE MORTALITY*, TUMOUR RECURRENCE[†] AND OVERALL PATIENT OUTCOME[‡]

Extent of resection	Peri-operative mortality [n (%)]	Operative survivors [n (%)]	Loco-regional recurrence [n (%)]	Distant metastasis [n (%)]	DWD [n (%)]	AWD [n (%)]	NED [n (%)]
TLP (n = 19)	–	19 (100)	6 (32)	5 (26)	7 (37)	4 (21)	8 (42)
TLPO (n = 16)	2 (12.5)	14 (87.5)	4 (29) [‡]	6 (43) [‡]	6 (43)	3 (21)	5 (36)
Total (n = 35)	2 (6)	33 (94)	10 (30)	11 (33)	13 (39)	7 (21)	13 (39)

*In 35 patients.

[†]In the 33 operative survivors.

[‡]One patient had both loco-regional and distant metastases.

TLP = total laryngopharyngectomy; TLPO = total laryngopharyngoesophagectomy; DWD = died with disease; AWD = alive with disease; NED = alive with no evidence of disease

lumen and then trying to pass a narrow bronchoscope over it and then down the oesophagus.⁴ Obviously, this manoeuvre is considerably traumatic and hazardous, with the possibility of tumour fragmentation and spread. Martins⁸ reported failure of distal oesophageal evaluation in examinations of 16 out of 34 patients (46 per cent) with pharyngoesophageal cancer, due to significant luminal obstruction. He proposed performing a total oesophagectomy in all cases in order to avoid the possibility of leaving tumour behind in the unexamined oesophagus.

In our present series, pre-operative endoscopic examination failed to evaluate the lower tumour limit as well as the condition of the distal oesophagus in 35 out of 61 patients (57 per cent) with hypopharyngeal cancer, due to significant obstruction. The high percentage reflects the late presentation of this disease seen in our country and thus the magnitude of the problem. The two pre-operative investigations performed (barium swallow and CT scanning), while able to evaluate the macroscopic lower tumour level in some cases, were able neither to accurately detect submucosal spread nor to reveal oesophageal skip lesions.

Submucosal tumour spread is one of the most difficult problems encountered during resection of hypopharyngeal cancers. The common belief is that such spread is not clinically detectable and that its extent and incidence are uncertain. Nevertheless, there are only a few studies^{1,9–11} reported in the English literature that estimate the true extent of such spread. These studies are summarized in Table III.

In 1997, Ho and colleagues¹ reported their detailed study of submucosal extension in 57 resected specimens by use of the whole-organ, step-serial

sectioning technique. They identified three types of submucosal tumour extension. Type I extension was characterized by a tumour with a smooth, round contour that extended from the main tumour bulk submucosally; the overlying intact mucosa was thereby elevated and was detectable on gross inspection at operation. In type II extension, tongues and islands of tumour infiltrated within the submucosa, unnoticeable on gross examination. Skip metastasis in the submucosa (i.e. submucosal tumour completely separated from the main tumour bulk) was classified as type III extension. Two-thirds of the submucosal extension found in this study was type I. Type II submucosal extension was found in only one-third of these authors' patients and usually occurred in those who had received radiotherapy before surgery (82 per cent). From these findings, Ho and colleagues¹ concluded that, contrary to common belief, submucosal tumour extension can readily be detected clinically, especially in patients who had not received pre-operative radiotherapy.

In our present study, IOOO was able to detect submucosal tumour spread in 86 per cent (19 out of 22) of cases in which it was demonstrated histopathologically. Since only 11 per cent (four out of 35) of our patients had received radiotherapy prior to surgery, most of the submucosal tumour extension in our patients must have been type I, by the system of Ho *et al.*¹ (i.e. noticeable on gross examination and thus endoscopically detected). The length of inferior submucosal extension in our series ranged from 4–28 mm and was thus comparable to the results of Davidge-Pitts and Mannel¹¹ and Ho *et al.*¹ but longer than the extension lengths found in other, older studies (Table III).^{9,10} Based on our IOOO results, two patterns of inferior submucosal spread were identified. In the majority of cases, the submucosal spread extended from the main tumour bulk and appeared endoscopically as an indurated area with an intact but elevated mucosa below the inferior limit of the tumour. In two cases, the submucosal tumour was completely separated from the main tumour bulk and presented on endoscopy as distinct satellite nodules in the distal thoracic oesophagus, i.e. skip lesions.

There has been a considerable amount of controversy in the literature about the necessity of total oesophageal resection in cases of advanced hypopharyngeal cancer.¹² Those in favour of TLPO have

TABLE III

STUDIES ON INFERIOR SUBMUCOSAL SPREAD IN HYPOPHARYNGEAL CANCER

Study	Patients (n)	Inferior submucosal spread (mm)
Hiroto <i>et al.</i> ⁹ (1969)	25	2–10
Harrison ¹⁰ (1970)	25	5–10
Davidge-Pitts & Mannel ¹¹ (1983)	14	6–30
Ho <i>et al.</i> ¹ (1997)	57	3–35
Present study (2006)	35	4–28

argued that the high incidence of multicentric tumours in these patients justifies resection of all the so-called 'condemned' upper laryngopharyngo-oesophageal mucosa.⁸ However, the higher peri-operative mortality as well as morbidity rates observed once the surgical resection is carried beyond the neck region into the mediastinum and abdomen have led most authors¹²⁻¹⁴ to refrain from performing unnecessary routine oesophagectomies in all patients.

Since distal assessment of the lower margin of the obstructing hypopharyngeal tumour was not possible pre-operatively in the cases included in this study, we used the results obtained from IOOO to decide whether or not the distal oesophagus could be safely preserved. The decision to preserve the thoracic oesophagus was taken only after ensuring that it was free of tumour and that the lower limit of the resection would be well above the suprasternal notch, thereby enabling a safe lower anastomosis between the transferred free flap and the remaining oesophageal stump lying within the confines of the neck. Using this technique, preservation of the thoracic oesophagus was achieved in more than half the cases, despite the advanced nature of the hypopharyngeal cancers included.

In 1998, Wei and colleagues¹⁵ published a large review of series reported over the previous 30 years which had included more than 10 patients undergoing TLPO and pharyngogastric anastomosis; they assessed a total of 978 patients. They noted an overall incidence of hospital mortality of 16 per cent (range, 0–50 per cent) and morbidity of 37 per cent (range, 4–55 per cent) for this operation. Wei⁵ thereby concluded that the surgical insult of this operation was significant and that it should only be performed for adequate tumour extirpation and not for the convenience of using the stomach for reconstruction.

In their clinical review of surgical resection in 109 patients with squamous cell carcinoma of the hypopharynx, Ho *et al.*¹⁴ showed that it was oncologically feasible not to remove routinely the whole length of the oesophagus; tumour recurrence rates and overall five-year survival rates did not improve with total oesophagectomy. On the other hand, the resection-associated complications were significantly higher in patients who had undergone an oesophagectomy in addition to a laryngopharyngectomy.

Our study further augments these previous observations. In the present series, hospital mortality occurred only in patients receiving a TLPO (two out of 16, 12.5 per cent). Our follow-up results (Table II), although preliminary and not representing long-term outcome data, similarly show that, in selected cases, local tumour control and patient survival did not significantly improve despite performance of a total oesophagectomy.

Conclusions

Intra-operative open oesophagoscopy was found to be a reliable method for lower margin and distal

oesophageal assessment in cases of advanced, obstructing hypopharyngeal cancers for which pre-operative endoscopy had failed to provide such information. The results obtained from this new intra-operative diagnostic modality can guide the surgeon as to the exact extent of resection needed to extirpate the disease. This can eliminate the need for unnecessary oesophagectomy in selected cases and thereby avoid its possible complications.

- **This article describes a new diagnostic modality, 'intra-operative open oesophagoscopy' (IOOO), proposed for distal endoscopic assessment of cases of advanced hypopharyngeal cancer with significant luminal obstruction**
- **The role of IOOO was evaluated in 35 cases of obstructing hypopharyngeal cancer operated upon over a four-year period**
- **The IOOO procedure was more accurate in evaluating inferior submucosal spread and in detection of oesophageal skip lesions than were routine pre-operative radiological investigations (barium swallow and computed tomography scans)**
- **The data obtained from IOOO determined the exact amount of inferior resection margin needed for tumour extirpation and allowed for a histopathologically negative margin in all cases**

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