

Although the definite risk factors are well known, it has been quite difficult to detect pharyngeal cancer at an early stage. Thus, most of the cases are diagnosed at an advanced stage and have a poor prognosis. In addition, the standard treatments of surgical resection and/or chemoradiotherapy worsen the patients' quality of life, resulting in speech defects, swallowing disorders, salivary disorders, and cosmetic deformities of the neck.

We previously reported that a new image-enhanced endoscopic technology,³ narrow-band imaging (NBI), was very useful for detecting these cancers at an early stage and that these superficial cancers could be treated with peroral endoscopic resection with minimal invasiveness.⁴⁻⁶ Shimizu et al⁷ and Iizuka et al⁸ also reported the usefulness of endoscopic resection for oropharyngeal and hypopharyngeal cancer. However, these reports included small numbers of patients, and their long-term outcome has not been reported. In addition, it seems to be premature to conduct a prospective study of peroral endoscopic resection for superficial pharyngeal cancer because its feasibility and safety have not been fully evaluated. In this study, we assess a large number of patients with a longer follow-up time to address the feasibility and usefulness of peroral organ-preserving endoscopic resection for superficial pharyngeal cancers.

PATIENTS AND METHODS

During the period from June 2002 to April 2008, 148 consecutive superficial oropharyngeal and hypopharyngeal cancers in 104 patients were treated by transoral organ-preserving pharyngeal endoscopic resection (TOPER) while under general anesthesia at National Cancer Center Hospital East and Kyoto University Hospital. Written informed consent for the treatment was obtained from all patients, and this study was approved by the local ethics committee.

Histological diagnosis of the lesions was made according to the World Health Organization classification of the tumor (head and neck tumors).⁹ Evaluation of the invasion of the tumor was also made according to the general rules for clinical studies of head and neck cancer by the Japanese Society for Head and Neck Cancer and the Japanese classification of esophageal cancer by Japan Esophageal Society.¹⁰ According to these guidelines, carcinoma in situ and subepithelial cancers are defined as a superficial cancer regardless of lymph node or distant organ metastasis. To date, there is no generally accepted definition of superficial cancer in this field. Thus, a cancer limited to the subepithelial layer of the pharynx is defined as superficial cancer in this study.

If the lesion was evaluated as carcinoma in situ or carcinoma with invasion to the subepithelial layer (not to the muscular layer), TOPER was indicated as a minimally invasive treatment (Fig. 1). Patients who received radiotherapy to the head and neck region previously

Take-home Message

- Peroral endoscopic laryngopharyngeal mucosal resection is a feasible and effective method for superficial pharyngeal cancer. This minimally invasive procedure can preserve the organ itself and is expected to improve the patient's quality of life and survival.

were not indicated. All patients refused radical surgical resection or chemotherapy or chemoradiotherapy. All lesions were detected by NBI with a magnifying endoscope and histologically confirmed by biopsy specimen as severe dysplasia/carcinoma in situ or squamous cell carcinoma.

TOPER was based on the methods of EMR using a cap (EMR-C)¹¹ or endoscopic submucosal dissection (ESD),¹² and the procedures were performed as previously reported^{11,12} by using a high-definition endoscope (Q240Z, Q260J, or H260Z; Olympus Medical Systems, Tokyo, Japan). For EMR-C, a soft food attachment (D-206-06; Olympus Medical Systems) to the tip of the endoscope was used. For ESD, an insulated-tip electro-surgical knife (IT knife; Olympus Medical Systems) was used. In both methods, the lesion was removed after inserting a needle beside the lesion and injecting an adequate volume of saline solution or glycerol containing diluted epinephrine (0.02 mg/mL) beneath the epithelium to lift it above the surrounding mucosa. We used a rigid laryngoscope (Nagashima, Tokyo, Japan) to obtain a sufficient working space by lifting the larynx. Iodine staining was used both to delineate the exact margin of the cancer lesion before resection and to detect residual lesion after resection. If a small residual lesion was endoscopically identified after EMR or ESD, argon plasma coagulation was done to prevent local recurrence. To check whether the larynx was swollen after resection, an endoscopic examination was performed on the day after resection with the patient under conscious sedation by periodic intravenous administration of pethidine hydrochloride (in total 0.5 mg/body weight). If the movement of the pharynx and larynx was unimpaired, the patient was encouraged to start eating semisolid food. If the larynx was swollen, the patient continued fasting until the swelling disappeared.

All resected specimens were cut into longitudinal slices measuring 2 mm in width. The slices were embedded in paraffin and stained with hematoxylin-eosin. All specimens were microscopically evaluated by 3 pathologists (S.F., A.Y., A. Ochiai) according to the World Health Organization classification.⁹

Follow-up endoscopy was performed after 1 to 3 months to check the healing of the mucosal defect and local residue after TOPER, and thereafter every 6 months to detect metachronous superficial cancer in

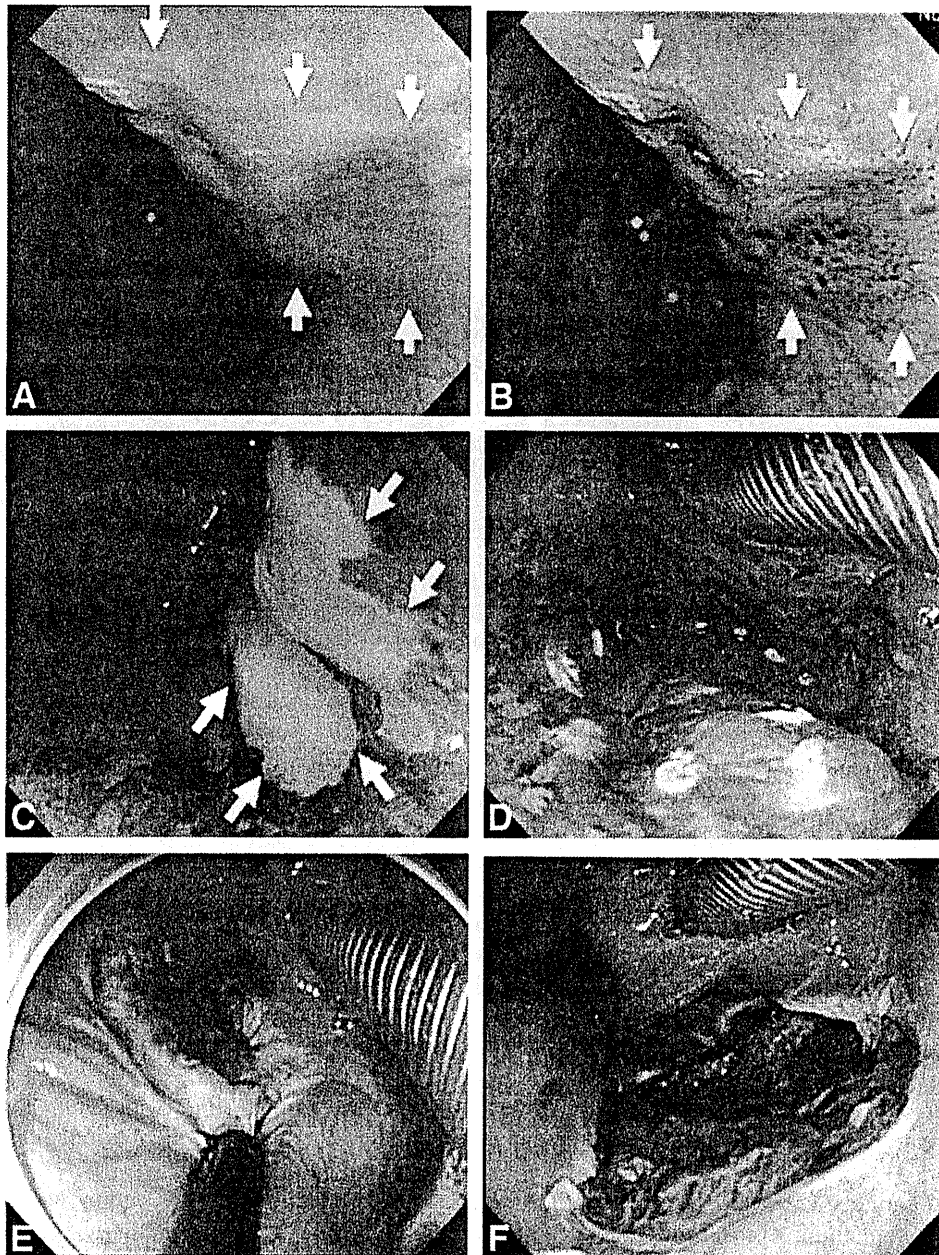


Figure 1. TOPER for superficial pharyngeal cancer. **A**, Endoscopic photograph showing the right piriform sinus with superficial pharyngeal cancer. The slight reddish-color mucosa is the neoplastic lesion (*arrows*). **B**, Narrow-band imaging corresponding with **A** showing well-demarcated brownish area (*arrows*). In the brownish area, tiny brown dots can be seen, which are irregular morphological changes in superficial microvessels in the neoplastic lesion. **C**, Iodine chromoendoscopy showing well-demarcated iodine voiding lesion (*arrows*). **D**, Marking around the lesion with a needle-knife with coagulation mode. **E**, Mucosal incision outside the marking after submucosal injection. **F**, The mucosal defect immediately after resection. **G**, Resected specimen with the neoplastic lesion in en bloc fashion. **H**, Histologically, this lesion was diagnosed as carcinoma in situ.

these regions. Local recurrence was defined as when the cancer was detected at the site of the TOPER scar. Patients underwent a CT scan of the neck, chest, and abdomen annually to detect lymph node and distant metastases.

StatView version 5.0 (SAS Institute Inc, Cary, NC) was used for statistical analysis. The results are expressed as median (range). The Fisher exact test was used to analyze

categorical data to compare proportions. Cause-specific and overall survival rates were estimated by using the Kaplan–Meier method.

RESULTS

Patient characteristics are shown in Table 1. They were predominantly male (97%), and the median age was 63

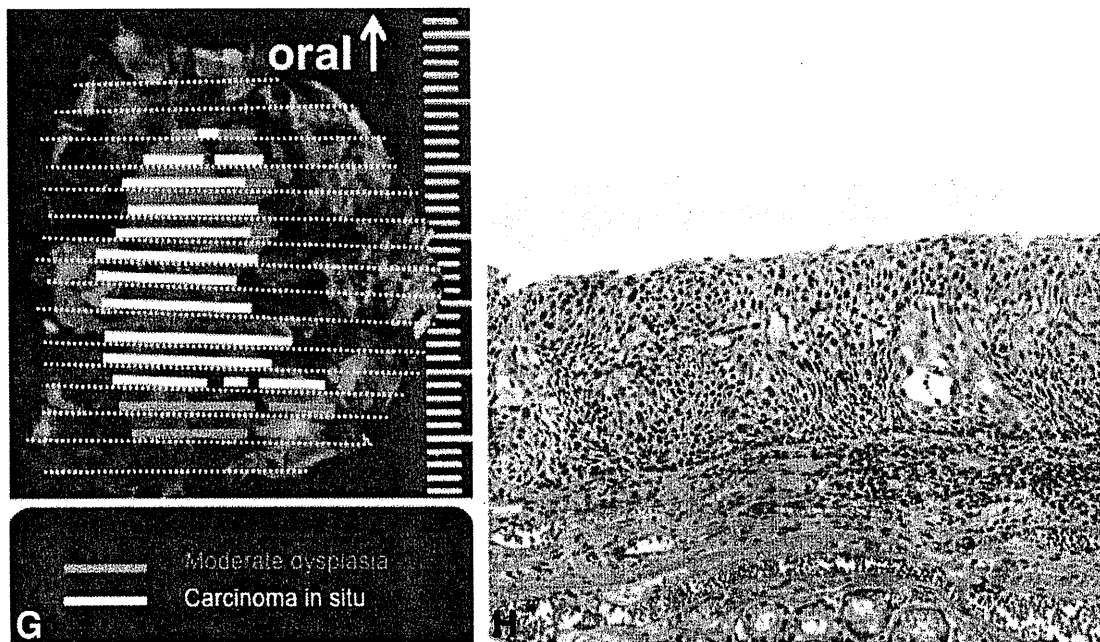


Figure 1. (continued)

years old (range 42-88 years). Of the 104 patients, 89 (86%) and 25 (24%), respectively, had esophageal cancer and/or head and neck cancer synchronously or previously. All of the cancers in the esophagus and the head and neck region were primarily treated with methods such as endoscopic resection, (chemo)radiotherapy, and surgery with curative intent. Most of the patients were identified as having cancer by follow-up examination for esophageal cancer or head and neck cancer. Of the 104 patients, 6 initially had unknown primary lymph node metastasis. Among them, the superficial lesion in the pharynx was finally found after radical dissection of the lymph node, and it was then treated by TOPER as a minimally invasive treatment.

Among the 104 patients, EMR-C method was indicated for 85 cases and the remaining 19 cases were indicated for ESD method. The selection was depended on the skill of the investigator. Before March 2006, all procedures of TOPER were performed by EMR-C method. After that, we turned to the treatment used by the ESD method for TOPER.

Lesion characteristics are shown in Table 2. Multifocal superficial cancer was found in 26 patients (25%). Nine lesions (6%) were finally diagnosed as severe dysplasia. Ninety-seven lesions (66%) were histologically confirmed to be carcinoma in situ, and the remaining 42 lesions (28%) showed slight invasion beneath the epithelium. The piriform sinus was the most frequent primary region (71%, 105/148).

The overall complication rate was 4.8% (5/104). Although subcutaneous emphysema developed in 2 patients immediately after the procedure, they improved

with conservative medical management within 1 week. Aspiration pneumonia developed after 1 patient started eating. This patient improved after intravenous administration of antibiotics. Delayed bleeding developed the day after resection in 2 patients. These patients were treated with endoscopic hemostasis. Temporary tracheostomy was indicated for 17 patients because their larynx was swollen and they were considered at risk of airway obstruction after extubation. All of the tracheostomies were closed within 2 weeks. No procedure-related deaths occurred.

The median fasting period after TOPER was 2 days (range 1-20 days). The median hospital stay after TOPER was 8 days (range 3-58 days).

The median follow-up period was 43 months (range 3-96 months). The overall survival rates at 3 and 5 years were 84% (95% CI, 77-92) and 71% (95% CI, 59-82), respectively (Fig. 1). Cause-specific survival rates at 3 and 5 years were 99% (95% CI, 97-100) and 97% (95% CI, 93-100), respectively (Fig. 2). Cumulative development of multiple cancers in the pharyngeal mucosal site at 3 and 5 years were 20% (95% CI, 10-29) and 22% (95% CI, 12-33), respectively (Fig. 3).

Patterns of recurrence and the clinical course are summarized in Figure 4. Of 104 patients, 96 (92%) had no recurrence in either the primary site or lymph node or distant metastasis. Although local recurrence developed in 6 patients at the primary site, 5 of them were cured by repeat TOPER. Although the remaining patient died of the disease, this patient had a history of surgical resection of large oropharyngeal cancer 3 months earlier. We then considered the cause of death of this patient as previous

TABLE 1. Patient characteristics (N = 104)

Sex, no.	
Male	101
Female	3
Age, y (range)	63 (42-88)
History of EC, no.	89
Treatment for EC, no.	
EMR including endoscopic treatment	39
CRT/RT	37
Surgery	13
History of HNC, no.	25
Treatment for HNC, no.	
RT	4
Surgery	21
Initial reason for detection, no.	
Discomfort of pharynx	6
Pretreatment detailed examination for EC	12
Follow-up after surgery for EC	10
Follow-up after CRT/RT for EC	27
Follow-up after EMR for EC	16
Follow-up after surgery for HNC	21
Follow-up after RT for HNC	4
Unknown primary lymph node metastasis	6
Screening for upper GI endoscopy	2
Method	
EMR-C	85
ESD	19

EC, Esophageal cancer; CRT, chemo/radiotherapy; RT, radiotherapy; HNC, head and neck cancer; EMR-C, EMR with a cap; ESD, endoscopic submucosal dissection.

oropharyngeal cancer. There was no difference in the local recurrence rate between EMR-C and ESD methods. Although lymph node metastasis in the neck developed in 2 patients, their superficial cancers were initially found during surveillance of the primary site of a lymph node metastasis of an unknown primary tumor. Thus, the possibility that the lymph node metastasis already existed before TOPER could not be excluded. Ninety patients (86.5%) had survived without disease at the time of this analysis. Although it was difficult to determine the direct cause of death in those who died, 10 patients were considered to have died of previous head and neck cancer or esophageal cancer rather than superficial pharyngeal can-

TABLE 2. Lesion characteristics (N = 148)

No. (%) of lesions per patient	
1	78 (75)
2	16 (15.4)
>3	10 (9.6)
Location of the lesions, no. (%)	
Oropharynx	20 (13.5)
Soft palate	1 (0.7)
Uvula	2 (1.4)
Posterior wall	10 (6.3)
Lateral wall	5 (3.4)
Vallecula	2 (1.4)
Hypopharynx	128 (86.5)
Left pyriform sinus	50 (33.8)
Right pyriform sinus	56 (37.8)
Postcricoid area	9 (6.1)
Posterior wall	13 (8.8)
Histological depth of the lesions, no. (%)	
Severe dysplasia	9 (6.1)
Carcinoma in situ	97 (65.5)
Carcinoma with subepithelial invasion	42 (28.3)

cer because the previous cancers were far advanced. Four patients died of other diseases.

DISCUSSION

This study demonstrates that peroral organ-preserving endoscopic resection for superficial pharyngeal cancer is a feasible treatment option with no severe adverse events and an extremely good prognosis. To our knowledge, this is the largest series of the patients to show the long-term effectiveness of endoscopic resection for superficial pharyngeal cancer. A recent report by Suzuki et al¹³ with 37 superficial pharyngeal cancers in 31 patients also showed the safety and effectiveness of endoscopic resection for these lesions. Until now, many patients with pharyngeal cancer were diagnosed at an advanced stage and thus required invasive surgery including the resection of the pharynx and larynx, resulting in speech defects and swallowing disorders, a major challenge from the aspect of the patients' quality of life. Our results demonstrating a new strategy of early detection and a minimally-invasive treatment for pharyngeal cancer are expected to be of great significance to these patients.

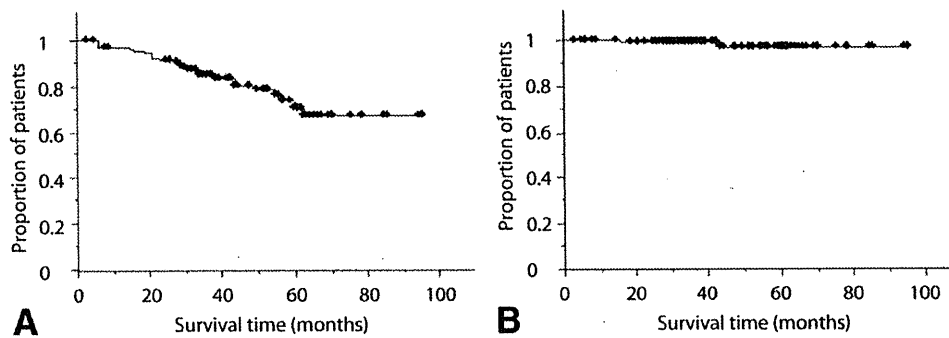


Figure 2. Overall survival (A) and cause-specific survival (B) after TOPER for superficial pharyngeal cancer.

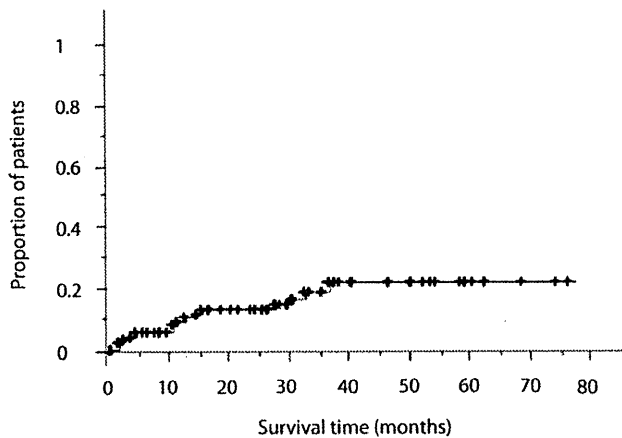


Figure 3. Metachronous development of superficial pharyngeal cancer after TOPER.

In the field of GI tract diseases, advances in the technology of endoscopic diagnosis have accelerated the detection of early cancer, leading to improvements in the technology of minimally-invasive endoscopic treatment such as EMR and ESD.¹⁴⁻¹⁶ Thus, EMR and ESD are now widely accepted as standard treatments for early cancer in the GI tract. In contrast, in the region of the oropharynx and hypopharynx, a reflection occurs at the time of endoscope insertion, causing pain and discomfort for patients. Therefore, this area has not been fully examined by routine endoscopic examination, even in the field of GI endoscopy. Furthermore, the resolution of the otolaryngeal endoscope was insufficient to identify a subtle change in the structure of the mucosal surface and microvasculature, which are important characteristics of superficial pharyngeal cancer. Thus, it has been almost impossible to detect early cancer in this region.

However, we previously reported that NBI combined with a magnifying endoscope enables early detection of pharyngeal cancer.⁴⁻⁶ Although this was a breakthrough in the diagnosis of cancer in the pharyngeal region, the treatment of superficial cancer has become a major issue because the standard treatment for pharyngeal cancer is surgery or chemoradiotherapy, which appears to be

overtreatment for these superficial cancers. Similar to the case for early cancer in the GI tract, endoscopic resection is the optimal treatment for superficial pharyngeal cancer because it is minimally invasive and curative. However, endoscopic resection for these lesions is not established as the first choice of treatment because it is not clear whether this treatment is feasible or improves the prognosis. Our results suggest that endoscopic resection could be the first choice of treatment for superficial pharyngeal cancer.

In carcinoma in situ, there is theoretically no risk of lymph node metastasis, but in pharyngeal cancers with subepithelial invasion, there is a risk of lymph node metastasis. However, we could not estimate the risk because we saw no cases of superficial cancer before NBI was developed. In our current analysis, lymph node metastases developed in 2 patients after TOPER. However, these patients had lymph node metastasis from an unknown primary tumor before endoscopic resection. Thus, the possibility could not be excluded that the lymph node metastasis existed before TOPER was recommended for them. Except for these patients with unknown primary lymph node metastasis, no lymph node metastasis developed in any patient in our series after TOPER. This result indicates that the risk of lymph node metastasis is quite low and thus prophylactic irradiation for cancers with subepithelial invasion appears unnecessary at this time, considering its disadvantages, including salivary disorders and mucosal inflammation.

In this study, multiple metachronous cancers at a pharyngeal mucosal site (22% at 5 years) developed in many patients. Suzuki et al¹³ reported that metachronous superficial pharyngeal cancer developed in 16% (5/31) of the patients. This possibly results from the “field cancerization” phenomenon.¹⁷ All patients included in this study were screened for the presence of multiple cancers by iodine staining of the entire pharynx when they underwent TOPER under general anesthesia. The fact that metachronous cancer frequently develops despite this screening suggests that the mucosa itself in this area has a high potential for cancer development. Therefore, close surveillance may be required after less invasive therapy that

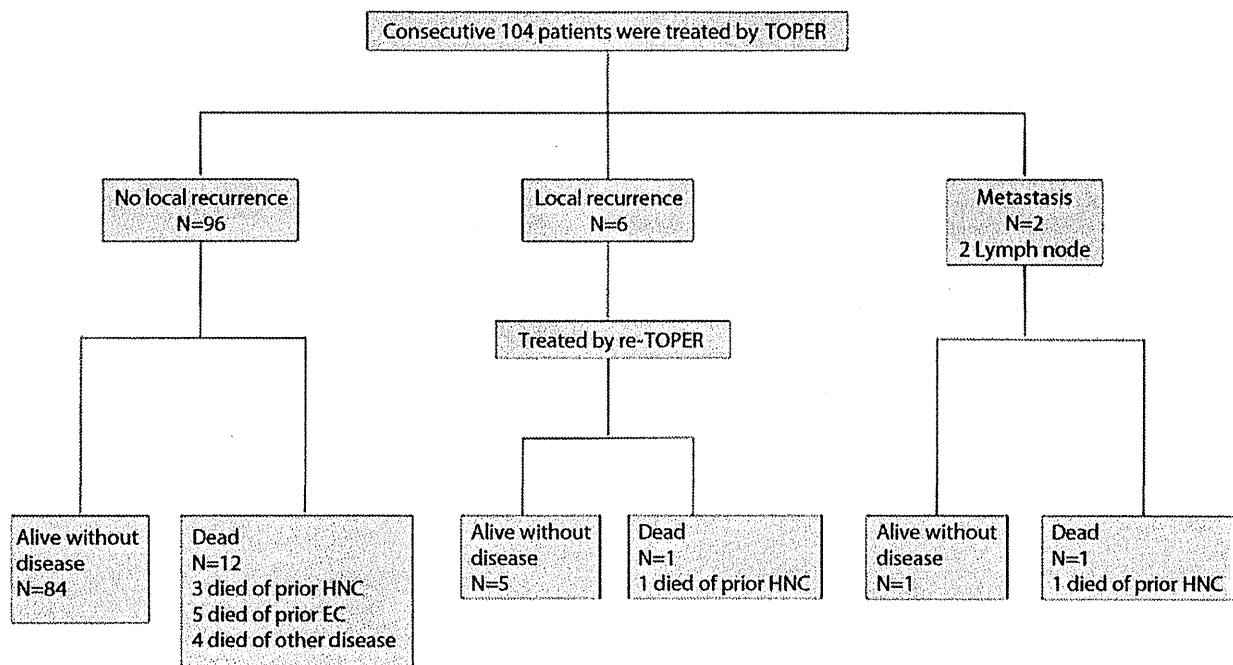


Figure 4. Clinical outcomes after TOPER for superficial pharyngeal cancer.

preserves the mucosa. Alternatively, if an effective prophylaxis were discovered, development of metachronous multiple cancers could be inhibited.

According to the TNM (tumor-node-metastasis) classification¹⁸ of pharyngeal cancer, the depth of tumor is unrelated to the staging, and the T number increases as the tumor size increases in cases of widespread superficial cancer. However, there is no risk of metastasis in intraepithelial cancer compared with invasive cancer of the same size, and, theoretically, the rate of lymph node metastasis is anticipated to be low, even in the case of microinvasive cancer. Thus, as many more superficial cancers are detected, a discrepancy becomes apparent between the current TNM classification system and actual clinical practice. In the future, the relationship between the depth of superficial cancer in the head and neck and the risk of lymph node metastasis, as well as its prognosis after endoscopic therapy, needs to be determined.

Generally, the survival of patients with multiple cancers is reported to be poor.¹⁹ However, the overall and cause-specific survival of the patients in this study could be regarded as acceptable because 93% (97/104) of the patients had a history of esophageal cancer or head and neck cancer and then would have poor prognosis. This result in part means that if the primary treatment succeeds with its curative intent, a second primary cancer should be detected at an earlier stage to obtain better survival. To date, there is no guideline for the optimal surveillance interval and the indication of TOPER. In addition, we have to determine the effective surveillance schedule and the limitations and indications for the TOPER method.

In conclusion, TOPER for superficial pharyngeal cancer is a feasible and effective treatment with curative intent. The strategies of evaluation of definitive risk (alcohol and smoking), identifying the superficial cancer by image-enhanced endoscopy, and minimally-invasive treatment by TOPER can provide a chance of organ preservation and survival for pharyngeal cancer patients.

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