

Research Article

Intraoperative Margin Assessment in Laser-Assisted Endoscopic Nasopharyngectomy

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Abstract

Background: Intraoperative consultation with frozen section is an important tool for evaluation of adequate surgical margins. Nevertheless, it is believed that frozen section analysis is less accurate in irradiated nasopharyngeal carcinoma (NPC) compared to other head and neck cancers. The current study was to investigate the accuracy of intraoperative consultation of irradiated NPC.

Methods: A total of 38 patients with irradiated NPC who had undergone endoscopic laser-assisted nasopharyngectomy for the period 2010 to 2022 were retrospectively analyzed. Results of intraoperative consultation of resection margins were reviewed. In addition, we performed a comparison of frozen section diagnoses between the current irradiated NPC cohort and an irradiated oral cavity cancer cohort.

Results: A total of 205 comparative sets of frozen section and permanent pathology results of nasopharyngectomy were used for analyses. The accuracy of intraoperative consultation was 100%. Nevertheless, 69 out of 205 intraoperative consultations resulted in a deferral of immediate diagnosis. The deferral rate was significantly higher than that of the comparative oral cavity cancer cohort ($P < 0.001$).

Conclusion: The current study demonstrated intraoperative consultation of irradiated NPC was challenging. In a significant number of specimens immediate diagnosis was difficult.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common head and neck cancer in Southeast Asia. The primary treatment modality for NPC is radiotherapy with or without chemotherapy. With advances in radiotherapy technique, the local control rate of NPC is currently excellent. Nevertheless, the management of locally recurrent NPC remains challenging [1]. The treatment modalities for locally residual or recurrent NPC include re-irradiation or salvage surgery. Endoscopic nasopharyngectomy is a feasible method which provides an excellent surgical route and avoids facial incision.

Current evidence has proved that salvage surgery can achieve a better survival rate for recurrent NPC and avoid severe complications associate with re-radiation. In a large series with 91 patients who underwent nasopharyngectomy, the 2- and 5-year overall survival rates were 64.8% and 38%, respectively [2]. In a retrospective study comparing recurrent NPC patients who received re-irradiation or salvage endoscopic surgery, patients who underwent endoscopic nasopharyngectomy

had better quality of life (QoL) than those who underwent re-radiation [3]. Another study prospectively enrolled 40 recurrent NPC and evaluated their QoL one year after endoscopic nasopharyngectomy. The authors reported that there were no significant differences in post-operative disease-specific QoL at 6 months and 1 year when compared to pre-operative QoL [4]. In the aforementioned study, the authors mentioned that subtotal resection negatively influenced post-operative QoL. Certainly, further treatment is indicated if total tumor excision cannot be achieved during the surgery. Intraoperative consultation with a pathologist regarding surgical margins is essential to determine clear resection margins of head and neck tumors. However, it is believed that frozen section analysis is less accurate in irradiated NPC. In 2014, Chan et al., conducted the first study investigated the accuracy of frozen section for locally recurrent NPC [5]. The authors reported that intraoperative consultation is useful for nasopharyngectomy but there were also significant limitations in frozen section analyses. In the following year, Chan et al. further reported that close and involved margins result in significantly inferior local tumor control and survival

in nasopharyngectomy patients [6]. In Chan's study, the patients received nasopharyngectomy via the maxillary swing approach [6]. Recently endoscopic nasopharyngectomy has become the mainstream for nasopharyngectomy. Electric cauterization or lasers, which are often used for tumor excision during endoscopic nasopharyngectomy, might impact on the quality of specimens for frozen sections. The purpose of the current study was to determine the accuracy of intraoperative consultation for nasopharyngectomy for irradiated NPC. In addition, we performed a comparison of frozen section diagnoses between an irradiated NPC cohort and an irradiated oral cavity cancer cohort.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of the study hospital (IRB No. CE21472A). All data were collected from a retrospective chart review. The IRB determined waivers of informed consent of the current study due to minimal risk to the study subjects. Patients who had local residual or recurrent NPC after standard chemoradiotherapy (rNPC) and then underwent laser-assisted nasopharyngectomy were identified from January 2010 to Aug 2022. Their demographic data, clinical outcome, frozen section diagnoses and the corresponding final histological results were obtained and analyzed. Oral cavity cancer is the leading head and neck cancer in Taiwan. The intraoperative consultation of irradiated oral cavity cancer is not as challenging as irradiated NPC in our pathologists' perspective. Therefore, we enrolled a comparison cohort of locally recurrent oral cavity patients (rOral Ca, local recurrence after primary surgery and adjuvant chemoradiotherapy) underwent salvage surgery during the same period. The comparison rOral Ca patients were consecutively collected from the Institutional Cancer Registry Database with matched numbers of frozen section with rNPC subjects. The surgical margins for frozen sections of rNPC were all obtained from the tumor bed. The frozen section specimens were sent to the pathologist right after being harvested. Tissues were embedded in optimal cutting temperature compound, frozen with liquid nitrogen, and cut. The pathologists immediately evaluated the slides and reported their findings to the surgeon. The tentative frozen section diagnoses included negative for malignancy, positive for malignancy, or deferral (atypical but inconclusive without further special staining). After the initial evaluation, the frozen section specimens were fixed in paraffin, then embedded and cut. The permanent pathological diagnoses were based on hematoxylin and eosin (H&E), and ancillary immunohistochemistry stainings. Although confirmed diagnoses could be made in most specimens, some remained inconclusive.

Based on the permanent pathological diagnoses, the true positive, false positive, true negative, false negative, and deferral rates of frozen sections were calculated. Chi square test was used to compare the frozen section results of rNPC patients with those of rOral Ca patients. Fisher's exact test was used to evaluate the correlation with resection margin involvement and local recurrence after nasopharyngectomy. The Kaplan-Meier method and log-rank test were used for analysis of the overall survival of the study subjects. Data are presented as median (range). All data were analyzed with GraphPad Prism 9.2.0 for Mac (GraphPad Software, San Diego, Ca, USA). P value < 0.05 was regarded as statistically significant.

RESULTS

From year 2010 to 2022, a total of 42 patients with irradiated NPC underwent nasopharyngectomy in the study institute. Four of them did not have an intraoperative consultation during the surgery and were excluded. Thirty-eight patients enrolled (27 males and 11 females) to the current study, with a median age of 48 (21-71) years old at NPC diagnosis. Their demographic data are shown in (Table 1). Twenty-eight rNPC patients were recurrent stage I, 5 were recurrent stage II, and the other 5 were recurrent stage IV [7]. Except for nasopharyngectomy, one patient had previous neck dissection, three had concurrent neck dissection, two had previous wedge resection of lung metastatic lesions, and one had subsequent radiotherapy for pelvic metastases. The median follow-up time after nasopharyngectomy was 31 (2-133) months.

All study subjects had received a nasopharyngeal biopsy confirmed locally residual or recurrence before nasopharyngectomy. The number of frozen sections performed during each surgical procedure was 5 (3-9) and were all for margin assessment. Two hundred and five pairs of frozen sections and the correspondent permanent pathology results of the rNPC patients were reviewed with two coauthors (pathologists, TYH and WCY) and analyzed.

Frozen section diagnoses of 38 rOral Ca patients were retrospectively collected from the Institutional Cancer Registry Database of the study hospital. In the comparative cohort, all rOral Ca patients were males, with a median age of 52 (35-73) years old. All enrolled rOral Ca patients had received both primary surgery and adjuvant chemoradiotherapy before the salvage surgery. Two hundred and one pairs of frozen sections and the corresponding permanent pathology results of rOral Ca patients were analyzed and compared with those of NPC patients.

Among the 205 frozen sections of irradiated NPC, there were 2 true positive and 134 true negative specimens, as well as 69 specimens for which the immediate diagnosis was deferred. The sensitivity, specificity, and accuracy of the 136 confirmed diagnosed frozen sections of NPC patients were all 100%. Among the 69 specimens that could not be determined immediately during the intraoperative period, 13 of them (18.84%) were positive, 51 (73.91%) were negative for tumor, and 5 (7.24%) remained undetermined due to severe tissue artifacts. Fifty-one out of the 69 deferred specimens required further ancillary immunohistochemistry studies for definite diagnoses. Eight out of the 13 deferred specimens that turned positive at final review, the pathologists mentioned crushing or cauterization artifacts seen in the tissue. Three representative cases are shown in (Figures 1-3). Nine out of the 38 NPC patients had resection margins involving tumor tissue according to the final pathological diagnoses. One had re-operation, one had re-operation as well as adjuvant chemotherapy, and the others received adjuvant chemotherapy. Four of the margin-involved patients had local tumor recurrence after nasopharyngectomy and adjuvant treatment. There was no significant correlation between margin involvement and local relapse at nasopharynx after nasopharyngectomy ($P = 0.174$).

Regarding to the results from the comparative rOral Ca, there were 201 pairs of frozen and corresponding permanent sections.

Table 1: The demographics of study subjects.

No	Sex	Age	Pathology	Initial stage	Recurrent stage ^a	Margin involved	Local recurrence ^b	FU ^c (mo)	Status
1	F	56	Nonkeratinizing carcinoma, differentiated	T2N2M0	rT1N0M0	Y	Y	69	NED
2	M	48	Nonkeratinizing carcinoma, differentiated	T3N1M0	rT2N0M0	N	N	4	DOC
3	F	46	Nonkeratinizing carcinoma, undifferentiated	T3N2M0	rT2N0M0	N	Y	69	A/W
4	M	48	Nonkeratinizing carcinoma, undifferentiated	T1N1M0	rT1N0M0	N	N	42	A/W
5	M	46	Keratinizing squamous cell carcinoma, poorly differentiated.	T3N2M0	rT1N0M0	N	N	91	NED
6	F	68	Nonkeratinizing carcinoma, undifferentiated	T1N1M0	rT1N0M0	N	Y	38	A/W
7	F	22	Nonkeratinizing carcinoma, undifferentiated	T1N0M0	rT1N0M0	N	N	62	NED
8	M	32	Nonkeratinizing carcinoma, differentiated	T2N2M0	rT1N0M0	N	N	61	DOC
9	M	45	Nonkeratinizing carcinoma, differentiated	T2N2M0	rT1N0M1	Y	N	19	DOD
10	M	56	Nonkeratinizing carcinoma, differentiated	T3N1M0	rT1N0M1	Y	Y	23	DOD
11	F	40	Nonkeratinizing carcinoma, differentiated.	T2N1M0	rT1N0M0	N	N	133	NED
12	M	38	Nonkeratinizing carcinoma, differentiated	T3N2M0	rT2N0M0	Y	N	95	NED
13	F	45	Nonkeratinizing carcinoma, differentiated	T2N2M0	rT2N2M1	Y	Y	16	DOD
14	M	54	Keratinizing squamous cell carcinoma, poorly differentiated	T3N2M0	rT1N0M0	N	N	116	NED
15	M	48	Nonkeratinizing carcinoma, differentiated.	T2N2M0	rT1N0M0	N	Y	88	DOD
16	F	50	Nonkeratinizing carcinoma, undifferentiated	T2N0M0	rT1N0M0	N	Y	93	NED
17	F	39	Nonkeratinizing carcinoma, undifferentiated	T2N3M1	rT1N0M1	N	N	31	NED
18	M	63	Nonkeratinizing carcinoma, undifferentiated	T1N0M0	rT1N0M0	N	N	21	NED
19	M	46	Nonkeratinizing carcinoma, differentiated	T1N0M0	rT1N0M0	N	N	10	NED
20	M	71	Nonkeratinizing carcinoma, differentiated	T3N2M0	rT1N0M0	Y	N	30	NED
21	M	48	Nonkeratinizing carcinoma, differentiated	T1N3M0	rT1N0M0	N	N	21	NED
22	M	42	Nonkeratinizing carcinoma, undifferentiated	T2N2M0	rT1N0M0	Y	N	87	NED
23	F	50	Nonkeratinizing carcinoma, undifferentiated	T1N1M0	rT1N0M0	N	N	32	NED
24	F	48	Nonkeratinizing carcinoma, undifferentiated	T1N1M0	T1N0M0	Y	N	32	NED
25	M	32	Nonkeratinizing carcinoma, undifferentiated	T1N1M0	rT1N0M0	N	N	28	NED
26	F	52	Nonkeratinizing carcinoma, differentiated	T1N0M0	rT1N0M0	N	N	48	NED
27	M	45	Nonkeratinizing carcinoma, differentiated	T3N1M0	rT1N0M0	N	N	14	NED
28	M	21	Keratinizing squamous cell carcinoma, moderately differentiated	T2N0M0	rT1N0M0	N	N	73	NED

29	M	58	Nonkeratinizing carcinoma, undifferentiated	T1N3M0	rT2N0M1	N	N	6	NED
30	M	56	Nonkeratinizing carcinoma, undifferentiated	T3N2M0	rT1N0M0	Y	Y	12	NED
31	M	41	Nonkeratinizing carcinoma, undifferentiated	T1N2M0	rT1N0M0	N	N	12	NED
32	M	48	Nonkeratinizing carcinoma, undifferentiated	T3N2M0	rT1N1M0	N	Y	12	NED
33	M	50	Nonkeratinizing carcinoma, differentiated	T3N1M0	rT1N0M0	N	N	48	A/W
34	M	43	Nonkeratinizing carcinoma, undifferentiated	T2N2M0	rT1N1M0	N	N	4	NED
35	M	55	Nonkeratinizing carcinoma, undifferentiated	T2N3M0	rT1N0M0	N	N	3	NED
36	M	69	Nonkeratinizing carcinoma, undifferentiated	T2N1M0	rT1N0M0	N	N	2	NED
37	M	50	Nonkeratinizing carcinoma, undifferentiated	T1N3M0	rT1N0M0	N	N	2	NED
38	M	66	Nonkeratinizing carcinoma, undifferentiated	T1N1M0	rT1N0M0	N	N	2	NED

^a Age diagnosis of NPC; ^a the 8th edition of the UICC/AJCC staging system⁷; ^b Local recurrence after nasopharyngectomy; ^c follow-up period after nasopharyngectomy; NED = no evidence of disease; A/W = alive with disease; DOC = dead of other causes; DOD = dead of disease

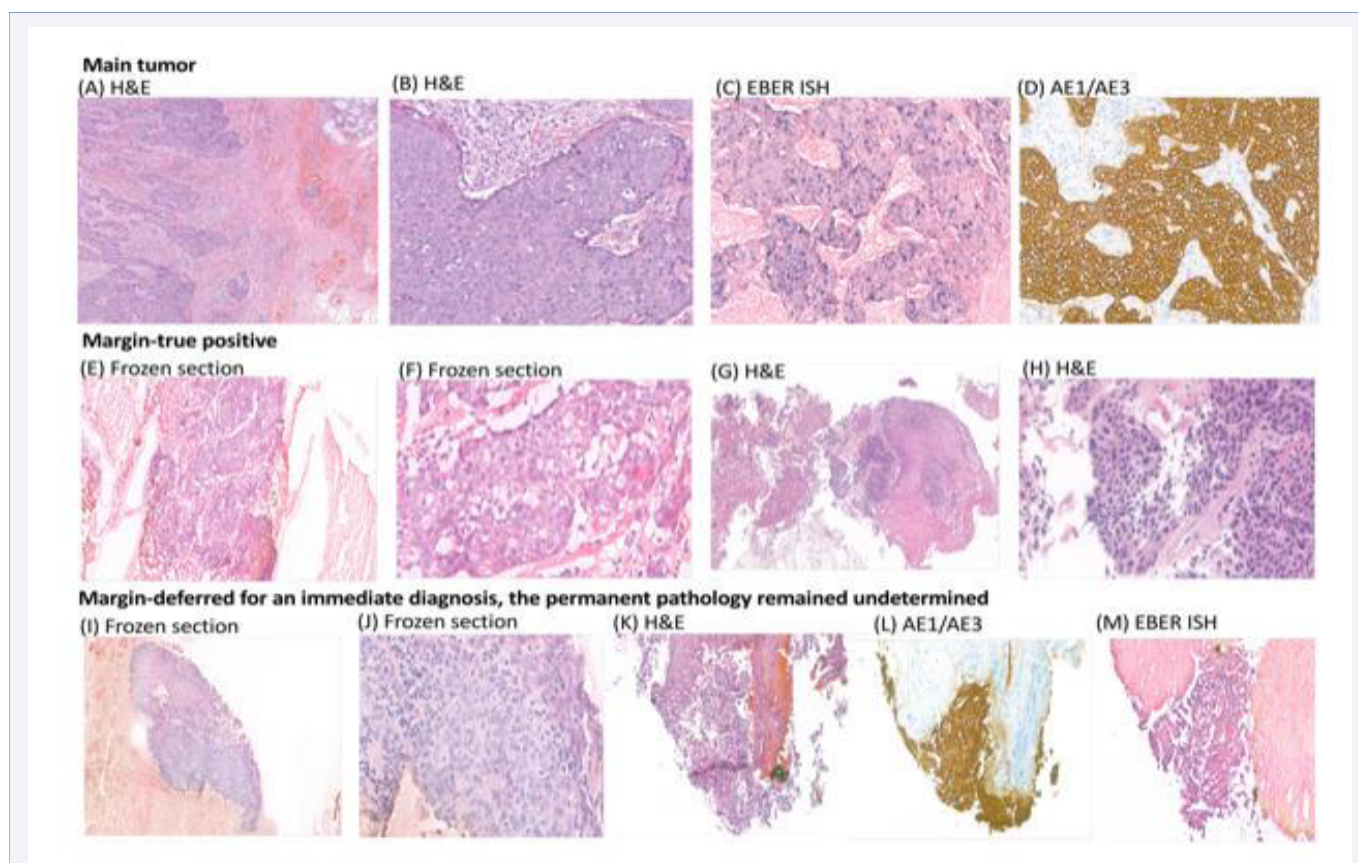


Figure 1 A gentleman was diagnosed with nasopharyngeal carcinoma (NPC) at 48 years old. Unfortunately, nasopharyngeal cancer recurred 5 years after chemoradiotherapy. The permanent pathology of excised tumor from nasopharyngectomy revealed a non-keratinizing carcinoma, with positive of AE1/AE3 immunochemistry staining (IHC) and in-situ hybridization (ISH) staining for EBER (A-D). One frozen section margin showed squamous mucosa with tumor growth in papillary pattern, accompanied by variable numbers of inflammatory cells infiltration. Most of the tumor cells were spindle shape, with a high nucleo-cytoplasmic ratio, contained hyperchromatic nuclei, and demonstrated little to absent keratinization (E-H). The other surgical margin showed atypical cells with marked cautery artifacts. Tentative intraoperative diagnosis was atypical cells with suspicion of malignancy. A definite diagnosis remained inconclusive even after IHC for AE1/AE3 and ISH of EBER on this severely crushed specimen (I-M).

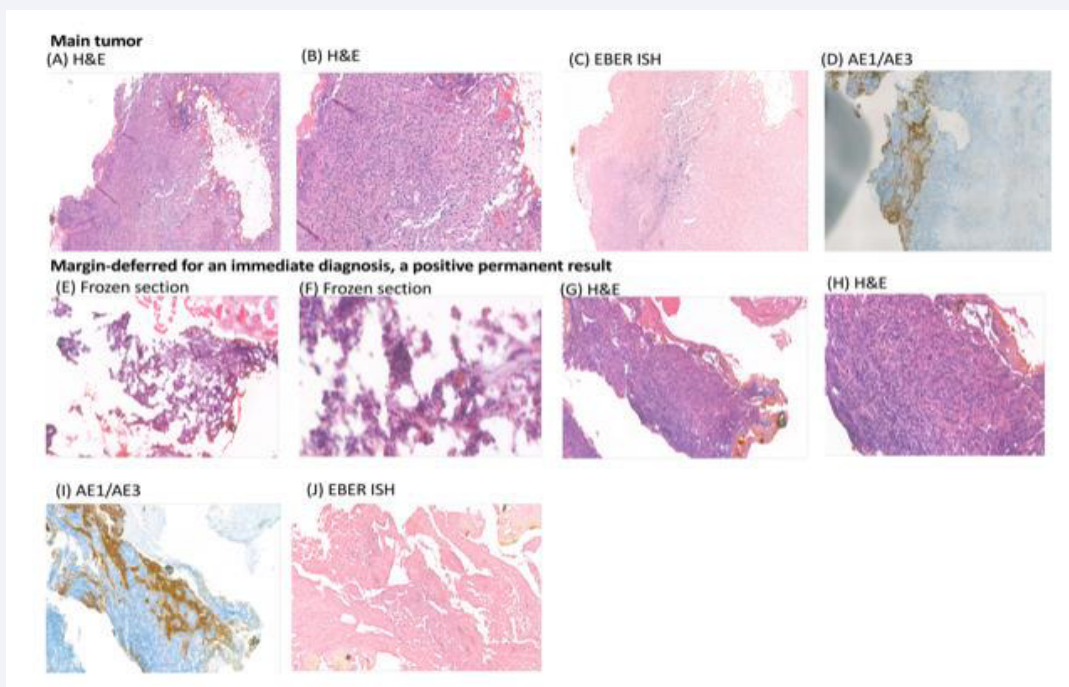


Figure 2 A 48-year-old female had residual NPC after chemoradiotherapy. The permanent pathology of excised tumor from nasopharyngectomy revealed a non-keratinizing carcinoma, with positive of AE1/AE3 IHC staining, and ISH stain for EBER (A-D). Immediate diagnosis was deferred for one of the resection margins: the frozen sections showed atypical cells with inflammatory cell infiltration in a fibrotic background. Those cells were confirmed to be malignant with the assistance of ancillary studies of IHC and ISH staining (E-J).

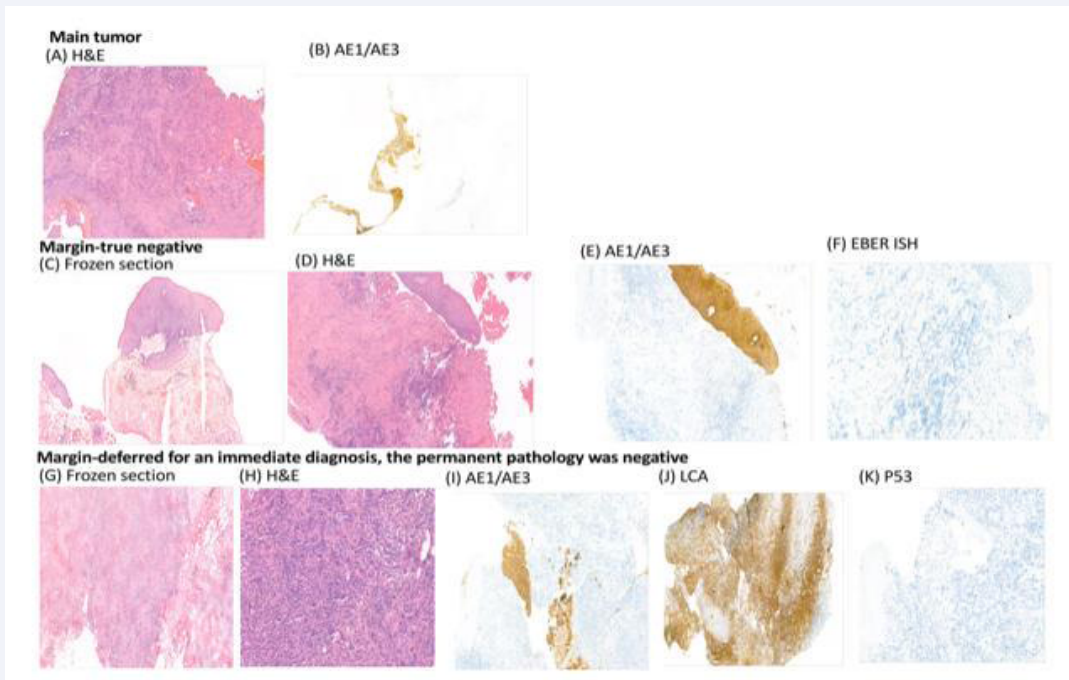


Figure 3 A 51-year-old female was diagnosed with locally recurrent NPC. She initially received salvage induction chemotherapy then nasopharyngectomy. The permanent pathology of excised tissue from nasopharyngectomy revealed complete response to induction chemotherapy and no residual tumor (A&B). One of the representative surgical margins demonstrated chronic inflammation and focal mild dysplasia of squamous epithelium and skeletal muscle. Ancillary studies of the permanent pathology show negative IHC staining for AE1/AE3 and negative ISH for EBER (E-F). Another surgical margin demonstrated marked lymphoplasmacytic inflammatory cells in the background with crush artifact. The tentative frozen section diagnosis during intraoperative consultation reported atypical cells. The permanent exam revealed lymphocyte infiltration and focal squamous epithelium in the specimen. Further IHC staining for AE1/AE3, LCA, and P53 revealed no malignant cells (G-K).

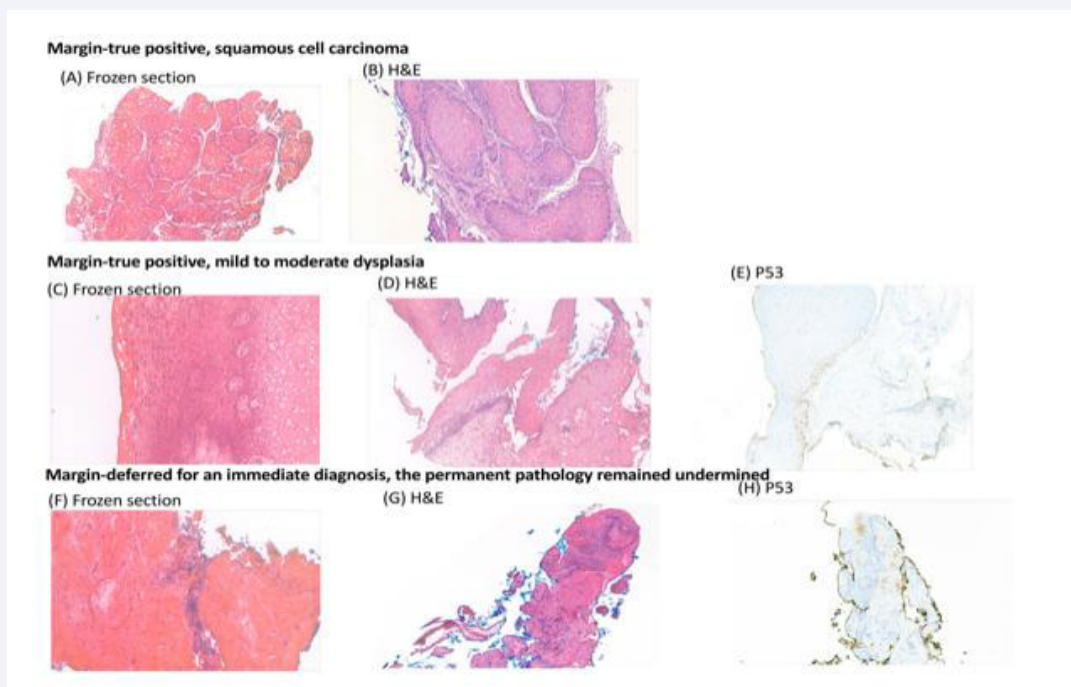


Figure 4 A 52-year-old male had oral cavity cancer with multiple primary sites including buccal mucosa, palate and gingiva. He had received primary surgery then adjuvant chemoradiotherapy. Nevertheless, local and neck recurrences occurred, and salvage surgery was then performed. One specimen was determined to be squamous cell carcinoma, moderately differentiated by both frozen section and permanent histological examination (A&B). Another resection margin was diagnosed as mild to moderate dysplasia. The permanent histology and ancillary immunochemistry studies revealed moderate epithelial dysplasia and focal increased p53 expression (C-E). The other resection margin could not be immediately diagnosed: the pathologist identified atypical cells identified in the specimen. Permanent histology examination with ancillary studies of AE1/AE3 and p53 staining revealed no malignant cells (F-H).

The sensitivity, specificity, and accuracy of intraoperative consultation for rOral CA are shown in (Table 2). There were 2 false positive, 27 true positive, 5 false negative, and 163 true negative results. Of note, there were only 4 (1.99%) specimens whose immediate diagnosis was deferred. The final pathological diagnoses of these 4 deferred frozen sections were 2 positive and 1 negative for tumor, while the other remained undetermined. A representative rOral CA case is shown in (Figure 4).

Comparing the accuracy of frozen section between the two cancer groups, there was a significant difference in accuracy between the two study cohorts ($P < 0.0001$, Table 3). There was a significantly higher proportion of specimens that could not be immediately determined during intraoperative consultation for irradiated NPC. Among the 205 resection margins from irradiated NPC, there were 15 surgical margins that were positive for tumor. Regarding rOral Ca, there were 33 out of 201 resection margins that were positive for tumors. Six patients underwent nasopharyngectomy died when the study finished. Four died of NPC progression, one died of second hematological malignancy, and the other died of pneumonia. The 2- and 5-year overall survival rates after the nasopharyngectomy in the current study were both 85.5%. The Kaplan-Meier curve of the survival of the study subjects are shown in Figure 5. Subjects with confirmed intraoperative frozen section diagnosis, resection margins clear of malignancy, no local relapse after nasopharyngectomy tended to have a better survival ($P = 0.084, 0.171, \text{ and } 0.557$, respectively). Nevertheless, only recurrent stage was a significantly predictive

factor for the overall survival after nasopharyngectomy ($P = 0.002$).

DISCUSSION

Intraoperative pathological consultation is a valuable method for determining adequate margins of cancer excision. The estimated accuracy of frozen-section diagnosis among experienced pathologists is over 90% [8,9]. In a prospective study published in 1991 by Zarbo et al., a large aggregated database from 297 institutes in the USA collected 79,647 frozen sections performed [8]. Of all the frozen sections performed in the aforementioned study, 4.2% were deferred, and the diagnostic concordance between frozen section results and the corresponding permanent pathology was 98.3% [8]. The frozen section deferral rate of Zarbo's study was slightly higher than that of irradiated rOral Ca (1.6%), but much lower than that of irradiated rNPC (32%) in the current study. Possible explanations for the difficulty in performing immediate diagnosis of frozen section of irradiated NPC include irradiation effect; crush tissue artifacts by cauterization or instruments, under-sampling, or characteristics of tumor entity. NPC is a tumor of epithelial origin secondary associated a benign lymphoid component [10]. As inflammation and infection are very common in the normal nasopharyngeal tissue, it makes the frozen section diagnoses difficult in NPC. Radiation results in histological changes including surface ulceration, epithelial atypia, submucosal fibrosis, vascular alternation, as well as atypical fibroblast and

Table 2: Comparison of the intraoperation responses between locally recurrent / residual nasopharyngeal carcinoma and locally recurrent oral cavity cancer.

	Nasopharyngeal carcinoma	Oral cavity cancer
Total frozen section (N)	205	201
Deferred immediate diagnoses (N)	69	4
Confirmed intraoperative responses (N)	134	197
Sensitivity	100%	84.36%
Specificity	100%	98.77%
Accuracy	100%	94%

Table 3: Comparison of accuracy of intraoperative diagnoses between locally recurrent / residual nasopharyngeal carcinoma and locally recurrent oral cavity cancer.

Class	Nasopharyngeal carcinoma		Oral cancer		
P value					<0.001**
frozen false positive	0		2	1%	
frozen true positive	2	0.98%	27	13.43%	
frozen false negative	0		5	2.49%	
frozen true negative	134	65.37%	163	81.09%	
defer	69	33.66%	4	1.99%	

Chi square test; ** P < 0.01

muscle degeneration could further adding difficulty [11]. We compared the results of frozen sections with irradiated NPC and irradiated rOral Ca in the current study. The results showed that the deferral rate was significantly lower in rOral Ca. Another explanation is the characteristics of tumor entity. NPC is classified into keratinizing squamous cell carcinoma and nonkeratinizing carcinoma (differentiated or undifferentiated) [10]. The incidence of non-keratinization NPC was significantly higher than that of keratinizing NPC in Taiwan [12]. Majority of oral cavity cancers are squamous cell carcinoma of the keratinizing type. The keratinization feature helps identify malignant cells in frozen sections.

Endoscopic nasopharyngectomy has been proved to be an effective salvage modality for rNPC [2]. Re-irradiation is associated with a high rate of complication like radionecrosis, cranial nerve palsy, or carotid blowout [13-15]. A recent multicenter, randomized controlled phase 3 trial in southern China enrolled 200 resectable locally recurrent NPC patients and assigned them to receive either endoscopic nasopharyngectomy or re-irradiation. The authors reported that endoscopic nasopharyngectomy significantly improved the 3-year overall survival compared with re-irradiation in patients with resectable rNPC (85.8% vs. 68%) [16]. Endoscopic surgery avoids facial scar and functional impact in comparison to open surgery. In addition, endoscopic surgery provides better visualization and differentiation between normal and diseased tissue when harvesting margins. Therefore, the incidence of positive margins in our results remained low. In the current results, we found the intraoperative consultation for frozen section was more challenging in rNPC than rOral Ca.

A tumor excision with negative surgical margins for tumor excision is an important prognostic factor for head and neck cancer treatment [17,18]. Head and neck tumor excision with tumor

involvement of resection margins was associated with adverse outcomes [6,19,20]. A Hong Kong study using open maxillary swing approach for nasopharyngectomy demonstrated negative impact of margin involved on outcomes [6]. Though some investigators had reported intraoperative gross examination by experienced surgeons made equal margin status with frozen section analyses [21], the use of frozen section to determine the margin status is highly recommended in oral cavity cancer excision [18,22]. In the current study, there were 9 patients whose resection margins were diagnosed with tumor involvement in the final pathological diagnoses. All received adjuvant treatment including re-surgery or chemotherapy. Our results demonstrated that aggressive adjuvant treatment after margin-involved nasopharyngectomy resulted in noninferior survival. Nevertheless, re-surgery or further adjuvant chemoradiotherapy could impact the QoL of patients. The difficulty of performing immediate diagnoses of frozen sections could be partially attributed to tissue artifacts caused by laser or electric coagulation and instrument crush. Eight out of 13 deferred frozen sections that turned positive at final review might related to crushing or cauterization artifacts in the tissue. A possible resolution is to re-sample margins to obtain better quality margins. The importance of communication between surgeons and pathologists in regards to intraoperative diagnosis has been discussed in the literature [17]. Immediately communication about tissue quality and re-sampling might reduce the deferred rate.

Although our study revealed a significantly high rate of deferred immediate frozen section diagnosis during endoscopic nasopharyngectomy for irradiated NPC, the excellent accuracy of frozen sections with a confirmed response indicates the value of intraoperative consultation. Confirmation of adequate margins could avoid normal tissue damage. Greater tissue loss in irradiated NPC increases the risk of osteoradionecrosis, possibly leading to neurovascular sequelae [13].

CONCLUSION

There were limitations to the effectiveness of intraoperative consultation for nasopharyngectomy of irradiated NPC. A significant number of surgical margins could not be determined immediately. The frozen section diagnosis for irradiated rNPC is challenging.

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AUTHOR CONTRIBUTION

Conceptualization: RSJ, KLL, CYW, CCW; drafting the manuscript: KHS, KLL; data collection and analyses: YHT, CYW, KLL; manuscript revision: RSJ, CCW.

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