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Radiotherapy for Stage I or II hypopharyngeal carcinoma

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Hypopharyngeal squamous cell carcinoma (HPSCC) is usually diagnosed at an advanced stage, and early-stage HPSCC is relatively rare. Because of the rarity of early-stage HPSCC, few reports have been published on the efficacy of radiotherapy (RT) in its treatment. We retrospectively reviewed the clinical records of 45 consecutive patients with Stage I and II HPSCC from May 1991 to June 2010. Patient characteristics were as follows: median age, 66 years (range, 44–90 years); male/female, 39/6; and T1/T2, 27/18. The irradiation dose ranged from 60 to 72 Gy (median: 70 Gy). Of the 45 patients, 21 underwent concurrent chemotherapy. With a median follow-up period of 62 months, the 5-year overall survival rate was 81%. Local failure occurred in 5 patients, and the 5-year local control rate was 83%. All local recurrences were successfully salvaged by surgery. The 5-year functional larynx preservation rate was 92%. Acute toxicity was manageable. Grade 3 laryngeal edema and Grade 3 hypothyroidism occurred in 1 patient each. No other late adverse events of Grade 3 or greater were observed. Based on these results, RT seemed to be an effective treatment modality for early HPSCC, with favorable organ preservation and acceptable adverse events. Early detection and accurate management of local recurrence and second malignancy was deemed to be critical.

Keywords: hypopharyngeal carcinoma; radiotherapy; chemotherapy; larynx preservation

INTRODUCTION

Hypopharyngeal squamous cell carcinoma (HPSCC) is usually diagnosed in the advanced stage, and early-stage HPSCC is relatively rare. In recent years, mainly owing to the development of laryngeal and gastrointestinal fiberscopes, HPSCC has tended to be found in an earlier stage. Although optimal treatment for early HPSCC has not been established, treatment options have included surgery and radiotherapy (RT) with or without chemotherapy. RT may be the treatment of choice in terms of functional preservation. However, because of the rarity of early-stage HPSCC, few reports have been published on the efficacy of RT. Nakamura *et al.* reported the results of chemoradiotherapy for early HPSCC [1]. In that article, chemoradiotherapy was started in the preoperative setting, and patients who achieved complete response after 30 to 40 Gy irradiation underwent further definitive chemoradiation. The authors reported equivalent disease-specific survival rates for early responders and for patients who underwent chemoradiotherapy and surgery. However, the effectiveness of curative chemoradiotherapy for all patient cohorts remains unclear. Nakamura *et al.* also reported the analysis of questionnaires from 10 institutions regarding early HPSCC treated with curative RT [2]. The authors collected the questionnaires from 115 patients treated between 1990 and 2001. The

results indicated the efficacy of RT for early HPSCC. However, deviation of treatment strategy might have existed in the multi-institutional questionnaire study. In our institution, definitive RT was performed as a first line treatment for Stage I and II HPSCC. Salvage surgery was performed for patients with local recurrence or non-responders. In this study, we retrospectively reviewed our single-institution results for definitive RT in Stage I and II HPSCC.

MATERIALS AND METHODS

Patients

From May 1991 to February 2010, 238 patients diagnosed with HPSCC were treated in our Division. Of these, 35 were treated with palliative intent, 2 preoperative, 73 postoperative, and 127 with definitive intent (82 Stage III/IV and 46 Stage I/II) (Table 1). Among the 46 patients with Stage I or II HPSCC, one patient was lost to follow-up after 4 months without any events. In this study, the remaining 45 patients with early (T1–2N0M0) HPSCC who underwent definitive RT were analysed. All patients were followed for at least 12 months or until any events. All patients had histologically proven squamous cell carcinoma. Patient characteristics are summarized in Table 2. There were 39 men and 6 women, with median age of 66 years (range, 44–90 years). Staging work-up included physical examination, laryngoscopy and computed tomography. Esophagogastroduodenoscopy was included as of May 2002, and PET scan was added in November 2006. According to the TNM classification of malignant tumors, 7th Edition [3], there were 27 patients with Stage I (tumor limited to one subsite of the hypopharynx and to ≤2 cm in the greatest dimension), 18 patients with Stage II (tumor that had invaded more than one subsite of the hypopharynx or an adjacent site or measured >2 cm but <4 cm in the greatest dimension, without fixation of the hemilarynx). The primary sites were the pyriform sinus in 35, the posterior pharyngeal wall in 6, and the postcricoid region in 4.

Table 1. Patient accrual according to treatment strategy and decade of accrual

	1991–2000	2001–10	Total
Preoperative	2	0	2
Postoperative	10	63	73
Palliative	17	18	35
Definitive (Stage III–IV)	15	67	82
Definitive (Stage I–II)	13	33	46[a]

[a]One patient was lost to follow-up after 4 months without any events and was excluded from this analysis.

Table 2. Patient characteristics

Characteristics	No. of patients
Total no. patients	45
Gender	
Male	39
Female	6
Age	
Median (range)	66 (44–90)
Tumor stage (from [3])	
Stage I	27
Stage II	18
Tumor differentiation	
Well	5
Moderately	15
Poorly	5
Unknown	20
Subsite	
Pyriform sinus	35
Posterior wall	6
Postcricoid region	4

Radiotherapy and chemotherapy

All patients underwent RT with radical intent, using 4-MV linear accelerator X-rays. No patient was treated with preoperative intent. A conventional fractionation schedule of 2 Gy/day was used. All patients received prophylactic lymph node irradiation. A prophylactic nodal area (including the retropharyngeal region and supraclavicular nodes) was irradiated up to 40–50 Gy with parallel-opposed lateral fields with a matched anterior lower neck field. The primary lesion was boosted with reduced fields after prophylactic nodal irradiation. The median total irradiated dose was 70 Gy (range: 60 to 72 Gy). Prescriptions for irradiation dose varied in accordance with the treating physician's preference. Concurrent chemotherapy was administered in 21 patients (Table 3). Inclusion criteria for chemotherapy were expanded to T2 disease beginning in the year 2000, and 16 out of 18 patients with T2 disease were treated after 2000; all 16 underwent concurrent chemotherapy. The two patients with T2 disease who were treated before 1999 did not receive chemotherapy. Five out of 27 patients with T1 disease underwent concurrent chemotherapy as per physician's preference. The regimen of chemotherapy is summarized in Table 4. Four patients received adjuvant chemotherapy with TS-1 (Oral fluoropyrimidine consisting of three components: tegafur, a prodrug of 5-FU; 5-chloro-2,4-dihydroxypyridine; and oxonic acid) (80 to 100 mg per body) as a part of feasibility study.

Follow-up

Patients were followed up monthly for the first year after completion of RT, every 3 months for the following 2 years, and then every 6 months until progression or death. Physical examination and laryngoscopy were performed at every visit. Computed tomography was performed 3 to 6 months after completion of RT, and thereafter performed annually. A PET scanner was installed in our Institute in 2005. PET scan was not performed routinely at follow-up examinations except in cases of suspected disease after computed tomography or physical examination. Esophagogastroduodenoscopy was performed at 1 to 2 year intervals, depending on the findings of routine follow-up examinations.

Statistical analysis

Survival was calculated from the date of initiation of RT to the date of any events or date last visited. Patients alive without relapse at the time of analysis were censored at their last follow-up. The progression-free survival (PFS) rate was calculated from the date of initiation of RT to the date of histologically-confirmed local recurrence, date of radiographic diagnosis of distant or nodal metastasis, or date of death from any causes. Local control rates and functional larynx preservation rates were calculated from the date of initiation of RT to the date of histologically-confirmed recurrence or date of surgical removal of larynx. Any death without local recurrence was censored for local recurrence. Any death with functional larynx was censored for functional larynx preservation rate. Survival rates were estimated using the Kaplan–Meier method. Univariate analyses with log-rank tests were performed to identify prognostic factors. Radiation dose, treatment interruption, use of chemotherapy, treatment period, tumor location, tumor stage, histological differentiation, age and gender were evaluated. All P values reported are 2-sided. For all statistical tests, differences were considered significant at the 5% level. Commercially available statistical software (StatView, 5.0; SAS Institute, Cary, NC) was used for analysis. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 [4].

Table 3. Irradiated dose and chemotherapy

	1991–2000 ($n = 13$)	2001–10 ($n = 32$)	total
Irradiated dose			
60 Gy	5	4	9
66–70 Gy	7	28	35
72 Gy	1	0	1
Chemotherapy			
Induction	0	0	0
Concurrent	2	19	21
Adjuvant	0	4	4

RESULTS

Survivals and larynx preservation

Median follow-up periods for surviving patients and all patients were 62 and 53 months, respectively (range, 12–132 months and 8–132 months, respectively). The 5-year overall survival rate and PFS were 81% and 69%, respectively (Fig. 1). Causes of death were: primary disease (1 patient), other primary cancers (5 patients) and suffocation from aspiration (1 patient). Of the 5 patients who died of other primary cancers, 2 died of synchronous cancer (lung cancer and esophageal cancer), 1 died of recurrent metachronous cancer before treatment of HPSCC (lung cancer) and 2 died of metachronous cancer which arose after completion of the treatment for HPSCC (esophageal cancer and oropharyngeal cancer). Local recurrence occurred in 8 patients, and the 5-year local control rate was 83% (Fig. 2A). All patients with local recurrence were successfully salvaged with surgical resection. Of these 8 patients, 3 were salvaged with laryngeal preservation surgery and 5 were salvaged with laryngectomy. Another 2 patients underwent laryngectomy because of second primary head and neck cancers (cervical esophageal cancer and oropharyngeal cancer). The 5-year functional larynx preservation rate was 92% (Fig. 2B). Three of 7 laryngectomies were performed more than 60 months after initiation of RT (66, 68 and 125 months, respectively). The 6-year

Table 4. Chemotherapeutic agents for concurrent chemoradiotherapy

Chemotherapeutic agents	1991–2000	2001–06	2007–10	total
Cisplatin (70–80 mg/m^2)	0	4	6	10
Nedaplatin (70–80 mg/m^2)	0	6	1	7
Cisplatin + 5-FU (Cisplatin, 70 mg/m^2 on day 1; 5-FU, 700 mg/m^2 on days 1–4)	1	2	0	3
Low-dose cisplatin (5 mg/m^2, daily)	0	1	0	1

5-FU = 5-fluorouracil.

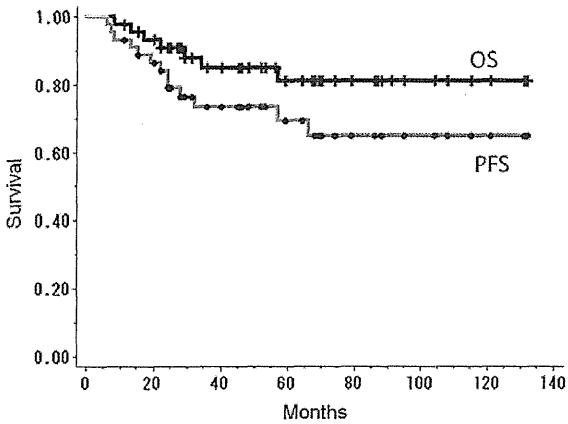

Fig. 1. Kaplan–Meier curves of overall survival rate (OS) and progression free survival rate (PFS). The 5-year overall survival rate and progression free survival rate for all patients were 81% and 69%, respectively.

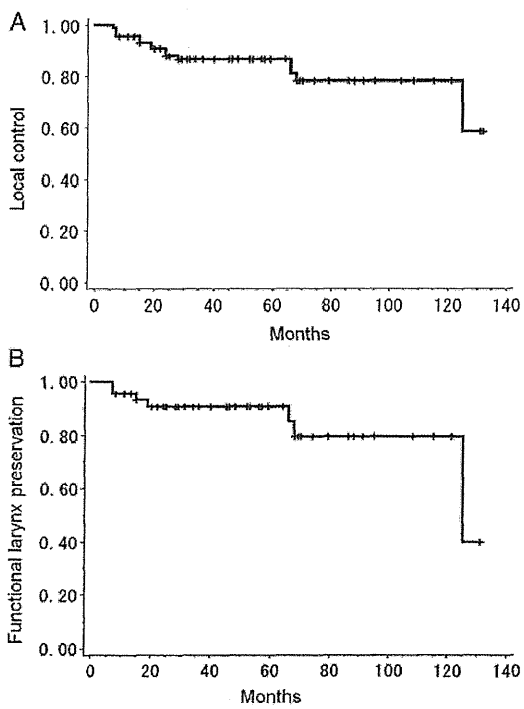

Fig. 2. Kaplan–Meier curves of (**A**) local control rate and (**B**) functional larynx preservation rate. The 5-year local control rate and functional larynx preservation rate for all patients were 83% and 92%, respectively.

functional larynx preservation rate was 79%. No cervical node metastasis was observed. Distant metastasis was observed in 1 patient.

Metachronous malignancies

Eight patients had previously treated metachronous malignancies before initiation of RT for HPSCC. All of these metachronous malignancies were judged to be cured at the time of initiation of RT.

Seven patients had synchronous malignancies. All of these malignancies were diagnosed at non-metastatic stages and were suitable for curative treatment. Six out of 7 synchronous malignancies were treated with RT concurrently with the HPSCC. One synchronous malignancy (esophageal cancer) was treated with endoscopic mucosal resection after completion of RT for HPSCC.

Fourteen patients developed metachronous malignancies in 17 sites during the follow-up period. Two patients received best supportive care (BSC). Patients in whom the other 15 malignancies were diagnosed without disseminated disease were treated with curative intent. Among 14 patients with metachronous malignancies after RT, 1 died of HPSCC, 2 died of metachronous malignancies, 1 died of suffocation from aspiration and 10 were alive and well at the time of analysis (Table 5).

Table 5. Synchronous and metachronous malignancies after radiation therapy

Synchronous malignancies	**No. of patients**
Esophagus	4
Larynx	2
Lung	1
Treatment	
RT	6
Endoscopic treatment	1
Metachronous malignancies after RT	No. of patients
Esophagus	6
Oropharynx	3
Lung	3
Prostate	2
Breast	1
Larynx	1
Hypopharynx[a]	1
Treatment	
Surgery	11
Endoscopic treatment	2
RT	1
Hormonal therapy	1
BSC	2

RT = radiation therapy, BSC = best supportive care.
[a]*De novo* carcinoma arising from contralateral pyriform sinus.

Table 6. Prognostic factors

Variable		5yr-PFS (%)	*P* value	5yr-LC (%)	*P* value
Dose	60 Gy	75	0.75	88	0.66
	66–72 Gy	68		81	
Interruption	< 5 days	74	0.18	84	0.55
	≥ 5 days	49		74	
Chemotherapy	yes	67	0.96	77	0.35
	No	73		87	
Period	1991–2000	62	0.41	68	0.16
	2001–10	72		89	
Subsite	PW	50	0.12	50	**0.01**
	Others	72		72	
Stage	I	67	0.84	80	0.93
	II	76		86	
Differentiation	w/d	0	**< 0.0001**	0	**< 0.0001**
	Others	77		91	
Age	< 70	65	0.43	80	0.61
	≥ 70	81		88	
Sex	Male	65	NA[a]	80	NA[a]
	Female	100		100	

PFS = progression free survival, LC = local control rate, PW = posterior wall, w/d = well-differentiated squamous cell carcinoma, NA = not assessed.
[a]*P* value was not assessed because no event occurred in the female arm.

Prognostic factors

We examined prognostic factors for PFS and local control, including radiation dose, treatment interruption, use of chemotherapy, treatment period, tumor location, tumor stage, histological differentiation, age and sex (Table 6). We found that well-differentiated squamous cell carcinomas ($n = 5$) were poor prognostic factors for PFS and local control ($P < 0.0001$). Tumors of the posterior wall ($n = 6$) were also associated with poor prognosis for local control ($P = 0.01$) (Fig. 3). The other factors did not show significant impact on PFS or local control.

Morbidity

No patient required a feeding tube or intravenous hyperalimentation during and after treatment. In the late period, laryngeal edema of Grade 3 (requiring temporal tracheostomy) was observed in 1 patient, and Grade 3 hypothyroidism (myxedema) was observed in 1 patient. The Grade 3 hypothyroidism was treated with levothyroxine sodium (Thyradin S). No other late toxicity of Grade 3 or greater was documented (Table 7).

Twenty-one patients underwent concurrent chemotherapy. Renal and hematologic toxicities related to chemotherapy were manageable (Table 7). Only 1 patient experienced febrile neutropenia.

DISCUSSION

Although several authors have reported the outcomes of RT for HPSCC, patients with Stage I and II hypopharyngeal cancer were relatively small cohorts in these studies [5–7]. In general, either RT or surgery with or without laryngeal preservation is selected as the initial treatment for T1–2 HPSCC. However, there have been only a few reports focusing on the efficacy of RT for early-stage hypopharyngeal cancer, and the optimal treatment approach remains controversial. RT has been recognized as an effective treatment modality for HPSCC. Mendenhall *et al.* achieved excellent local control in 80% of patients with T1–2 pyriform sinus carcinoma treated with RT alone [5]. Later, Amdur *et al.* also reported the results of RT for T1–2 pyriform sinus [6]. They included 101 patients with T1–2 carcinoma of the pyriform sinus and achieved local control rates for T1 and T2 tumors of 90% and 80%, respectively. However, of 101 patients, only 25 patients had Stage I or II disease. Their report showed relatively poor 5-year overall survival rates (57% for Stage I, 61% for Stage II, respectively). It was

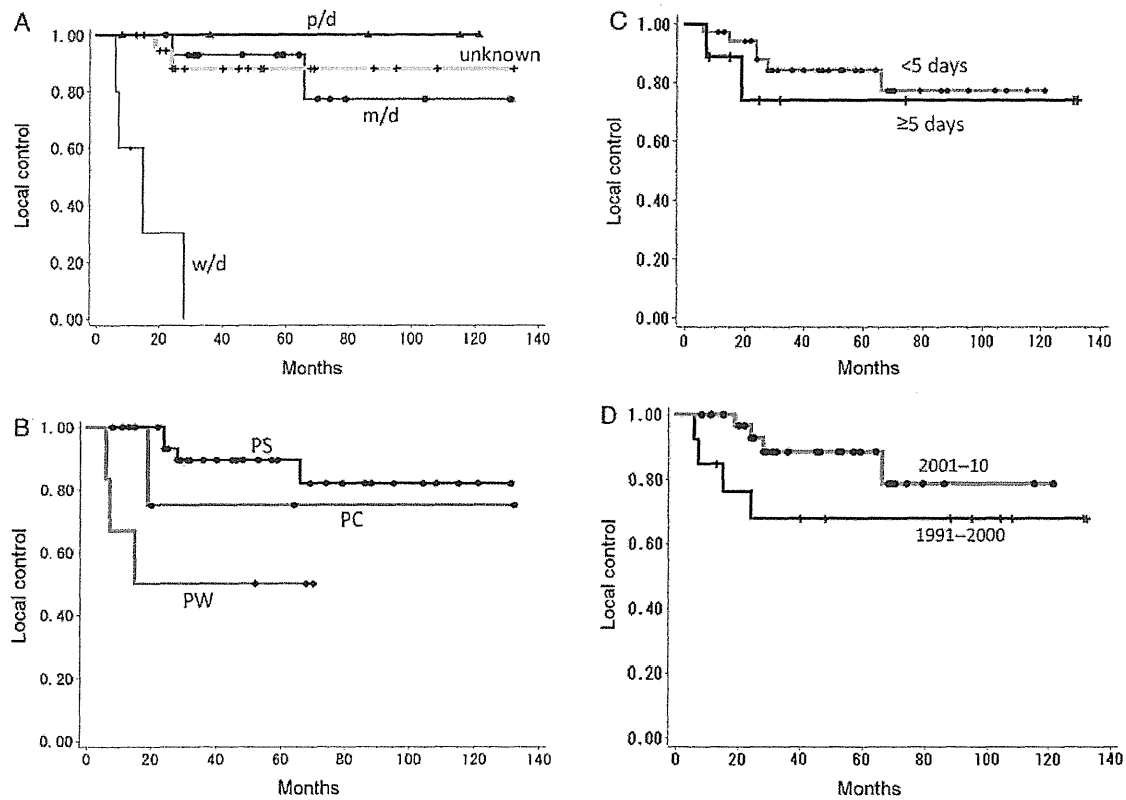

Fig. 3. Kaplan–Meier curves of local control rate according to (**A**) histological differentiation, ($P < 0.001$), (**B**) tumor location ($P = 0.01$), (**C**) treatment interruption ($P = 0.55$), (**D**) treatment period ($P = 0.16$). p/d = poorly differentiated squamous cell carcinoma, m/d = moderately differentiated squamous cell carcinoma, w/d = well-differentiated squamous cell carcinoma, PS = pyriform sinus, PC = postcricoid region, PW = posterior wall.

Table 7. Toxicity profiles (grade 3/4 toxicities)

Concurrent Chemotherapy	**yes ($n = 21$)**	**no ($n = 24$)**
	No. of patients (%)	**No. of patients (%)**
Early		
Renal dysfunction	0 (0)	0 (0)
Neutropenia	4 (18)	0 (0)
Anemia	0 (0)	1 (4)
Thrombocytopenia	2 (9)	0 (0)
Febrile neutropenia	1 (4.5)	0 (0)
Late		
Thyroid dysfunction	0 (0)	1 (4)
Laryngeal edema	0 (0)	1 (4)

difficult to determine the long-term efficacy of RT for early-stage HPSCC. Garden *et al.* reported that the 2-year actuarial local control rate for T1 and T2 tumors after RT alone was 89% and 77%, respectively [8]. These reports included patients with neck node metastasis, and neck nodes were managed with or without neck node dissection. Because these reports contained node-positive patients, the survival period was short. It may be difficult to elucidate the exact long-term benefit of RT for node-negative HPSCC, although these reports suggest the efficacy of curative RT for primary lesions. In our series, definitive RT resulted in a comparable local control rate (83%) in a neck node-negative patient cohort that achieved a relatively longer overall survival rate of 81% with a median follow-up period of 62 months.

In our series, all patients received prophylactic nodal irradiation and no patient experienced cervical node metastasis. Compared to other reported series for early stage HPSCC (Table 8), the nodal control rate in our study seemed to be favorable. There appears to be some potential benefit of prophylactic irradiation for early stage HPSCC. Local recurrence occurred in 8 patients. The incidence of local recurrence was comparable to other studies. All local recurrence was successfully salvaged with surgery. Early detection and adequate management for local recurrence seemed to be critical.

Table 8. Comparison of prophylactic irradiation, loco-regional control, and salvage surgery

Series	Treatment period	No. of Pts	median f/u (M)	5yr-OS (%)	Prophylactic RT yes/no	Prophylactic dose (Gy)	No. of nodal rec.	No. of local rec.	No. of salvage sx for local rec.
Nakamura[a] [1]	1976–2002	43	52	70	35/8 (81%)	30–50	3 (7%)	2 (5%)	2 (100%)
Nakamura[b] [2]	1990–2001	115	47	66	90/25 (78%)	36–50	14 (12%)	30 (26%)	26 (87%)
Yoshimura [10]	1988–2007	77	33	47	66/11 (86%)	20–50	11 (14%)	16 (21%)	12 (75%)
Current study	1991–2010	45	53	81	45/0 (100%)	40–50	0 (0%)	8 (18%)	8 (100%)

[a]Eleven of 43 patients received surgery after 30–40 Gy irradiation.
[b]Questionnaire collected from 10 institutions.
Pts = patients, f/u = follow-up period, M = months, OS = overall survival rate, RT = radiation therapy, rec. = recurrence, sx = surgery.

In our series, 5 patients died of second primary cancers. Yoshimura *et al.* also reported a high incidence of synchronous and metachronous malignancies [9]. In their report, patients with metachronous malignancies had poorer survival outcomes. In our series most metachronous malignancies were diagnosed at non-metastatic stages, and curative treatments were performed. Out of 14 patients with second malignancies, 9 were successfully treated and were alive and well at the time of analysis. We believe close follow-up and accurate management of local failure and metachronous malignancies can provide better outcomes. Careful follow-up and early detection of local recurrences and other malignancies are critical for survival and larynx preservation.

Several authors have reported the additional benefit of chemotherapy for advanced head and neck cancers [10–13]. However, the additional benefit of chemotherapy for early HPSCC remains controversial. Use of concurrent chemotherapy for these tumors differed among the reported articles. While Yoshimura reported that only 16 of 77 patients received concurrent chemotherapy [9], Nakamura reported that 39 of 43 patients received concurrent chemotherapy [1]. Inclusion criteria for concurrent chemotherapy were not documented in these articles. In our series, the treatment strategy included concurrent chemotherapy for T2 disease beginning in the year 2000. Chemotherapeutic agents were varied during the two decades of our study period. Since 2007, cisplatin alone has been the mainstay in our Institute. Out of 18 patients with T2 disease in our series, 16 were treated after 2000. All 16 underwent concurrent chemotherapy. In our results, T2 disease had a local control rate comparable with that of T1 disease. Thus, there may be some potential benefit of chemotherapy for T2 disease. T2 disease has a relatively wide range of tumor sizes (2 to 4 cm) and it may prove that concurrent chemotherapy is beneficial for larger tumors. However, it is still difficult to address the exact benefit of chemotherapy because of small sample sizes and lack of randomized data. Though adverse events related to chemotherapy were manageable, it is important to avoid unnecessary use of chemotherapy in patients who are likely to have tumor control with RT alone.

Well-differentiated squamous cell carcinoma and posterior wall tumors had poor outcomes for local control. Though these patients were a small cohort in our series, the poorer local control in posterior wall tumors was compatible with the report of Yoshimura *et al* [9]. Exact reasons for the poorer outcome in posterior wall tumors and well-differentiated tumors remain unclear. We might consider a more aggressive treatment strategy for these kinds of high-risk tumors, such as concurrent chemotherapy or volume-reduction surgery prior to RT.

Several authors have reported results of laryngeal preservation surgery for selected patients [14–17]. Though these reports also include node-positive disease, and it would be difficult to compare the long-term efficacy and local control rate with our result, they seemed to obtain comparable local control rates. However, postoperative mortality and morbidity is not negligible. Postoperative death rates of 2 to 10% were reported, and persistent swallowing difficulties and speech impairment were also reported. Radical RT for early-stage HPSCC may have some mortality and morbidity advantage in treatment without reducing local tumor control.

No patients in our series were treated with intensity-modulated RT (IMRT). IMRT is a conformal RT technique that can spare the major salivary glands and may reduce the incidence of long-term radiation-induced xerostomia. All patients with preserved larynxes in our series maintained ability in speech and swallowing. However, lack of saliva affects quality of life (QoL). Recently, the result of a randomized trial comparing conventional RT and parotid-sparing IMRT for head and neck cancers was reported [18]. Parotid-sparing IMRT was found to reduce the incidence of xerostomia and improve QoL. Because of the expected longer survival for early HPCSS, IMRT may be beneficial and should be considered for these patients.

CONCLUSION

In conclusion, RT for early HPSCC is deemed to be a feasible and effective treatment modality with minimal morbidity. In our cohort, 81% 5-year overall survival and 91%

functional larynx preservation rates were obtained during a follow-up period of 62 months. Salvage surgery with or without larynx preservation was reserved for recurrent disease. Early detection and adequate management of local recurrence and metachronous malignancies are critical in obtaining longer survival.

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C 下咽頭がん

2. Planned Neck Dissection の EBM とは？

❶ 序論

Planned Neck Dissection（PND）は 1986 年に Mendenhall ら[1]が報告した頸部リンパ節転移陽性頭頸部がんに対する治療戦略である．原発巣が放射線療法により制御可能と判断され，なおかつ頸部リンパ節転移巣の制御が放射線療法では困難と推測される症例をその治療対象としている．リンパ節に対する治療が奏効したかどうかにかかわらず，放射線治療終了後に急性期反応の消退を待って，放射線治療前からの計画どおりに頸部郭清術を行うため，その戦略的側面から planned neck dissection とよばれる．本邦では計画的頸部郭清術という表現が用いられることが多い．

下咽頭がんに対する治療戦略として，同時併用化学放射線療法（concurrent chemoradiotherapy: CCRT）の占める割合は近年増加しているが，従来より原発巣と比較して頸部リンパ節転移巣の制御は不良なことが知られている．下咽頭がんに対する PND は，放射線治療の弱点を観血的に補完して頸部のコントロールを改善することを目的としており，CCRT と併せて行うことにより喉頭温存治療の一翼を担うものである．

❷ 指針

下咽頭がんにおいては，原発巣が比較的限局している状態でもすでに頸部リンパ節転移をきたしていることがまれではない．したがって下咽頭がんに対する PND の最もよい適応となるのは，原発巣と頸部転移巣の組み合わせが下記のような症例である．

原発巣: 手術による喉頭温存は困難であるが CCRT による制御が十分に期待される，T2 症例と一部の T3 症例，手術を希望しない T1 症例．

頸部転移巣: 化学放射線療法での制御が困難と思われる N2-3 症例．

T4 症例では原発巣の制御が不安定であるため慎重にならざるを得ない．また N 0-1 症例では一般的に PND の必要性は指摘されていない．通常は原発巣が CCRT により消失していることを確認したうえで，CCRT 終了後 4〜12 週目に奏効の有無を問わず頸部郭清術を施行する．

❸ エビデンス

1 頭頸部がんに対する PND の有用性

Grabenbauer ら[2]は口腔がん，中下咽頭がんに対する CCRT 後の頸部リンパ節再発は下咽頭がんで最も多く，下咽頭がんに関しては PND を含めた積極的な治療が必要であると報告している．また Argiris ら[3]は，N2-N3 頭頸部がんに対して PND を行うこ

とで少なくともlocoregional control rateを改善すると報告しており，さらにBrizelら[4]はPNDが生存にも寄与すると報告している．Mukhija[5]らは根治的な照射後であれば，選択的頸部郭清でも全頸部郭清と同等の成績が得られると報告している．

2 CCRT後完全奏効症例への対応

Lavertuら[6]の報告では，N2-3症例のPND切除標本で，照射後に完全奏効と判定された群で22%，非完全奏効群で47%にpathological positive nodeを認めたとしている．Corryら[7]は，頸部リンパ節のみに再発してくる症例は少なく，通常は遠隔転移を伴って再発してくる場合が多いと報告している．同様にFerlitoら[8]は，PNDが有用とする24の報告とPNDの有用性は低いとする26の報告を分析し，結論としてCCRTで完全奏効した症例では頸部単独で再発をきたす割合は低く大部分で遠隔転移を伴うため，PNDを漫然と施行するべきではないと結論づけている．

3 再発確認後に行う救済手術との比較

Mabantaら[9]は頸部リンパ節転移の増悪確認後では多くの症例（65%）で救済手術が行えないと報告しており，Stensonら[10]やLavertuら[11]はPNDの方が合併症は少なく，頸部再発後の救済手術のほうが合併症の頻度が高いとしている．

4 CCRT後の画像診断

Brizelら[4]は，臨床評価と病理学的結果は必ずしも相関しないと報告している．またFDG-PETについて，Schechterら[12]はCCRT後に腫瘍へのFDGの集積低下があるため偽陰性となることがあると報告しており，一方でTanら[14]はPETでの陽性所見よりもむしろ陰性所見が頸部コントロールの予測に重要であると報告している．Gourinら[15]は，SUV（standardized uptake value）と病理組織学的所見あるいはリンパ節サイズに関連は認められなかったと報告しており，CCRT後の画像評価法として支持されるには至っていない．

5 NCCN（National Comprehensive Cancer Network）ガイドライン（2009）

下咽頭癌T1, N+; T2-3, any N症例において，同時併用化学放射線療法により原発巣と頸部リンパ節転移巣が完全奏効した場合，頸部リンパ節に対して最低でも12週毎のPET，CE-CTかMRI，診察を行い，転移が出現しなければ経過観察を，転移が確認されれば頸部郭清術を行うよう推奨している．ただしT1N1症例やT2-3N0-1症例もこのカテゴリーに含まれており，またPNDについては触れられていないため，参考にとどめる．

❹ 根拠となった臨床研究の問題点と限界

そもそも大部分の報告においては検討の対象となる原発巣が多岐にわたっており，そのデータを下咽頭がんにそのまま当てはめることができない，また後向きの検討が大部分であり，前

向きの臨床研究も必要であろう．対象症例中に占める下咽頭がん症例の割合が低い報告では，特にその解釈に注意を要する．また放射線治療における技術的な問題として，中咽頭がんでは原発巣と頸部転移巣を含めた標的体積に均一に根治線量を投与することが比較的容易であるが，対側を含めた多領域への転移をきたしやすい下咽頭がんでは標的体積の凹凸や頭尾側方向の長さから線量分布が不均一となり，さらに危険臓器の線量制約から頸部転移巣への十分な線量投与が困難な場合があることもあげられる．

CCRT後の頸部再発症例では遠隔転移を伴っていることも多く，PNDが大きく生存率に寄与するというエビデンスを得ることは困難であろう．しかしながら非生存例に対する配慮が切り捨てられるべきではない．すなわち，PND施行例と非施行例では再発から死に至るまでの臨床経過やQOLが異なってくる可能性が浮かび上がってくる．頸部再発がもたらす本人・家族・医療従事者らの苦痛（疼痛・出血・悪臭・処置）については，臨床研究などでは通常あまり取り扱われず評価されない．

5 患者に適応する際の注意点

前述したように，文献によって対象患者が大きく異なっており治療強度も違うため，PNDの施行あるいは省略にあたっては各施設で行っている化学放射線療法がどの報告文献と合致あるいは類似しているかを十分に比較検討すべきである．また放射線治療は我々が漠然と想像しているほど均てん化されたものではなく，導入機材や放射線治療医によって照射野や照射線量の配分が異なることに注意を払う必要がある．一連の治療の中にPNDを組み込むのか，あるいはあくまで照射での完全奏効を目標とするのか，放射線治療医との協議をできれば十分に行いたいところである．併用する化学療法の種類や併用回数についてもしかりである．

明らかな頸部再発を確認した後に施行する救済手術では，照射後早期に施行するPNDと比較して線維化や瘢痕化が高度であり，合併症の増加のみならず手術手技的にも困難な傾向がみられる．PNDを施行するにあたっては，治療開始以前からその長所・短所を十分に理解しておく必要がある．

6 コメント

近年の放射線治療では抗がん剤の併用や照射技術の向上に伴って局所頸部制御率は上昇し，画像診断技術の向上により照射後転移診断の精度も改善されつつある．今後はさらなる診断・治療技術の向上により，真にPNDを行うべき症例を絞り込んで不必要な手術は省略すべきとの方向に戦略は変換されていくであろう．しかしながらASCO（American Society of Clinical Oncology）の喉頭がんに対する機能温存治療ガイドライン[13]にある下記内容について，2006年の報告ではあるがその思考課程や患者対応を含めて治療者は十分に留意すべきと思われる．

「根治的放射線療法や化学放射線療法を受けたN2, N3症例に対する手術は，その反応いかんによらず推奨される．一部の外科医や患者は手術に伴う死亡リスクや大部分の症例で病理組織学的検索により転移がないことが見込まれることを根拠として頸部郭清術に対し意欲的ではないが，照射後という状況下の転移診断に関して意志決定に明確に寄与し得る標準的な画像評価法は確立されていない．またこのような状況下で頸部再発に対して行われる救済手術は，成

功に導かれる可能性が低い，上記の二点については，放射線治療もしくは化学放射線治療により臨床上完全奏効と判断されて希望的に経過観察を選択したすべての患者と討論しておくべきである.」

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〈岩江信法〉

頭頸部癌 36(1)：89-92, 2010

中・下咽頭癌に対するplanned neck dissectionにおけるリンパ節転移残存状況に関する検討

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要旨

当院では2001年12月以降，中・下咽頭癌に対して，Platinum + 5FUの導入化学療法後，T1/T2症例とT3の導入化学療法奏功例を主な対象として同時併用化学放射線療法を根治目的で施行し，N2以上のリンパ節転移陽性症例に対してはさらにplanned neck dissectionを積極的に施行してきた。当初患側のレベルⅠ～ⅤまたはⅡ～Ⅴ領域の郭清を行ってきたが，郭清リンパ節の病理組織学的検討で，初回治療前の画像検査で転移が疑われた領域以外にはviable cellの残存を認めないことが分かった。planned neck dissectionでは，郭清範囲を治療前転移陽性レベル周辺に限局して縮小できる可能性があるものと思われた。

キーワード：同時併用化学放射線療法，計画的頸部郭清術，中咽頭癌，下咽頭癌，腫瘍残存リンパ節

Investigation of residual cancer node levels in planned neck dissection after concurrent chemoradiotherapy for oropharyngeal and hypopharyngeal cancer:

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Summary

We investigated four patients with oropharyngeal cancer and 12 patients with hypopharyngeal cancer who underwent planned neck dissection (PND) after concurrent chemoradiotherapy (CCRT) from December 2001 to January 2005. We performed neck dissections in levels Ⅰ to Ⅴ or Ⅱ to Ⅴ. But we found that there was no residual cancer in the initially negative neck level. We conclude that we can limit the excision in the initially positive level in planned neck dissection.

Key words：Concurrent chemoradiotherapy (CCRT), Planned neck dissection (PND), Oropharyngeal cancer, Hypopharyngeal cancer, Residual cancer nodes

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はじめに

当院では中・下咽頭癌に対して，原則としてまずPlatinum + 5FUの導入化学療法を施行し，その4週後にT1，T2症例の一部に放射線療法，その他の症例には根治手術を行ってきた。2001年12月以降は同時併用化学放射線療法(concurrent chemoradiotherapy: CCRT) とCCRTでの制御が困難と思われるN2以上のリンパ節転移陽性症例に対するplanned neck dissection (PND) を積極的に施行している。今回我々は，初回治療前に把握していた転移陽性リンパ節と，PNDでviable cellの残存が病理組織学的に確認されたリンパ節を，所属レベル単位で比較して検討した。郭清範囲縮小の妥当性の可能性とあわせて文献的考察を加え報告する。

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表 1 化学療法 ICT，CCRT に共通

70 歳未満		70 歳以上	
Ccr ≧ 80ml/min		Ccr ≧ 80ml/min	
CDDP 80mg/m^2	day1	CDDP 60mg/m^2	day1
5FU 1000mg/body	day1-5	5FU 800mg/body	day1-5
Ccr < 80ml/min		Ccr < 80ml/min	
CBDCA	day1	CBDCA	day1
5FU 1000mg/body	day1-5	5FU 800mg/body	day1-5

対象および方法

導入化学療法（induction chemotherapy: ICT）は CDDP 80mg/m^2 day1，5FU 1000mg/body day1～5 を施行した。70 歳以上の症例では CDDP 60mg/m^2 day1，5FU 800mg/body day1～5 に減量し，腎機能低下が認められる場合は，CDDP の代わりに CBDCA（AUC 4～5）を用いた（表 1）。原則として ICT 奏功症例を CCRT の対象としたが，非奏功例でも強く希望する場合には対象に含めた。また治療方針が当初から CCRT で確定している症例の一部で ICT を省略した。CCRT の際には，放射線治療開始日にあわせて同内容の化学療法を 1 クールのみ同時併用した。放射線治療は全頸部に 45.0～50.4Gy/25～28Fr 照射後，原発巣と転移陽性リンパ節に 26.0～20.0Gy/13～10Fr を追加照射し，総線量約 70Gy とした。CCRT による粘膜炎や皮膚炎などの急性期反応の沈静化を待ち，なおかつ原発巣再発が無いことを確認した後，6～10 週目を目途に PND を予定したが，状況に応じて手術時期を遅延した。T4 any N 症例および T1-3 N0-1 症例では，CCRT 終了後 PND を施行せずに経過観察とした（図 1）。

PND 施行当初（中咽頭癌症例 1，2，下咽頭癌症例 1，2）はレベルⅠ～Ⅴを郭清範囲としていた。その後は原則としてレベルⅡ～Ⅴを郭清範囲とし，もしレベルⅠへの転移や他領域からまたがる進展（中咽頭癌症例 3，下咽頭癌症例 9）を認めていればレベルⅠ領域の郭清を追加した。N2c 症例で一側のリンパ節転移が単発性かつ最大径が 3 cm 以下の場合（下咽頭癌症例 6，7，10）は，同側の郭清を省略した。なお頸部リンパ節転移の有無の評価には CT，MRI および超音波検査を用いたが，検査により評価が異なる場合は特に超音波検査を重視して総合的に判断した。

上記の郭清範囲で PND を施行した中咽頭癌症例（2001 年 12 月から 2004 年 7 月の間に初回治療を開始したもの）は 4 例 4 側，下咽頭癌症例（2001 年 12 月から 2005 年 6 月の間に初回治療を開始したもの）は 12 例 13 側であった。これら計 16 例 17 側を対象として検討をおこなった。

摘出リンパ節は最大割面で切り出しを行い，H-E 染色で viable cell 残存の有無および角化物や壊死物，石灰化，線維化，異物反応などの癌細胞の転移があったことを示唆する所見の有無を確認した。

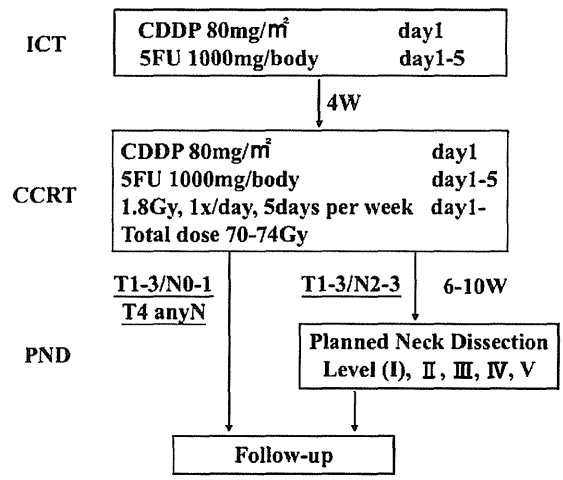

図 1 当院の ICT/CCRT/PND

結 果

PND を施行した中咽頭癌 4 例，下咽頭癌 12 例の年齢，性別，亜部位，TN 分類，初回治療前転移把握レベル，治療効果，郭清範囲，病理組織学的腫瘍瘢痕残存レベル，病理組織学的 viable cell 陽性レベル，レベル別リンパ節検索個数を示す（表 2，表 3）。

中咽頭癌では 4 症例 4 側中の 2 側（50%），下咽頭癌では 12 症例 13 側中の 9 側（69%）に viable cell の残存を認めた。viable cell は初回治療前に転移を把握していたレベルの全てあるいは一部に限局しており，その他のレベルに viable cell を認めなかった。viable cell が認められなかったレベルでも，角化物や壊死物，石灰化，線維化，異物反応などの癌細胞の転移があったことを示唆する腫瘍瘢痕の所見は大部分の症例で確認されたが，すべて治療前に転移を把握できていた範囲内であった。

下咽頭癌では，治療前レベルⅡ転移陽性が 11/13（85%）と最も多く，次いでレベルⅢ転移陽性が 10/13（77%）であった。PND 後の viable cell の残存状況は，治療前の転移陽性状況と比較すると，レベルⅡが 6/11（55%），レベルⅢが 5/10（50%），レベルⅣが 2/7（29%），レベルⅤが 3/4（75%）であった。

表 2　中咽頭癌 PND 施行症例頸部リンパ節転移状況

症例	TN	治療前転移把握レベル	治療効果 ICT/CCRT	郭清範囲	病理組織学的腫瘍癒痕残存	病理組織学的 viable cell 陽性	レベル別リンパ節数 viable cell 陽性／提出リンパ節
1. 60男	側壁 T2N2b	II, III, IV, V	NC/PR	I, II, III, IV, V	II	II, III, IV, V	I (0/5), II (1/6), III (2/2), IV (1/4), V (1/7)
2. 78男	前壁 T2N3	II	NC/PR	I, II, III, IV, V	II	なし	I (0/4), II (0/3), III (0/3), IV (0/10), V (0/7)
3. 61男	後壁 T1N3	I, II, III, IV, V	−/PR	I, II, III, IV, V	I	なし	I (0/7), II (0/1), III (0/0), IV (0/3), V (0/7)
4. 69男	前壁 T2N2b	II, III, IV	NC/PR	II, III, IV, V	なし	IV	II (0/3), III (0/7), IV (1/9), V (0/29)

治療効果（ICT/CCRT）は，リンパ節に対する評価のみを記す。

表 3　下咽頭癌 PND 施行症例頸部リンパ節転移状況

症例	TN	治療前転移把握レベル	治療効果 ICT/CCRT	郭清範囲	病理組織学的腫瘍癒痕残存	病理組織学的 viable cell 陽性	レベル別リンパ節数 (viable cell 陽性数／提出リンパ節数)
1. 79男	ps T2N2a	II	−/NC	I, II, III, IV, V	II	II	I (0/0), II (1/8), III (0/6), IV (0/1), V (0/5)
2. 57男	psT2N2b	II, III	−/PR	I, II, III, IV, V	II, III	II	I (0/0), II (1/7), III (0/5), IV (0/6), V (0/1)
3. 54男	psT3N2b	II, III, IV	NC/PR	II, III, IV, V	II	II, III	II (2/3), III (1/2), IV (0/3), V (0/3)
4. 66男	psT1N2a	II	−/PR	II, III, IV, V	II	なし	II (0/5), III (0/2), IV (0/3), V (0/6)
5. 56男	psT3N2b	II, III	PR/CR	II, III, IV, V	II	III	II (0/9), III (2/3), IV (0/6), V (0/6)
6. 57男	psT3N2c	右：II, III, IV, V 左：III	−/CR	II, III, IV, V 施行せず	III, IV, V	なし	II (0/3), III (0/12), IV (0/14), V (0/36)
7. 64男	pwT3N2c	右：II, III 左：II	PR/NC	II, III, IV, V 施行せず	II	II	II (1/1), III (0/6), IV (0/5), V (0/8)
8. 85男	psT2N2b	II, III, IV, V	NC/PR	II, III, IV, V	II, III, IV, V	II, III, IV, V	II (6/7), III (9/10), IV (7/7), V (8/8)
9. 56男	psT2N3	III	−/PR	I, II, III, IV, V	II	III	I (0/2), II (0/4), III (2/2), IV (0/4), V (0/2)
10. 57男	pcT3N2c	右：II, III, IV 左：II	PR/CR	II, III, IV, V 施行せず	II, IV, V	なし	II (0/6), III (0/3), IV (0/5), V (0/7)
11. 80女	pwT3N2c	右：II, III, IV, V 左：II, III, IV, V	NC/PR NC/PR	II, III, IV, V II, III, IV, V	II, III, IV, V III, IV, V	II, V III, IV, V	II (1/3), III (0/1), IV (0/1), V (3/4) II (0/1), III (6/9), IV (4/5), V (3/4)
12. 66男	psT3N2a	II	−/NC	II, III, IV, V	II, III, IV, V	なし	II (0/7), III (0/2), IV (0/8), V (0/3)

治療効果（ICT/CCRT）は，リンパ節に対する評価のみを記す。

考　察

1986年にMendenhall[1]等が始めて報告したPNDについては，その必要性や合併症に関する議論が賛否両論存在する。Kailash[2]等は放射線治療でcomplete responseが得られた症例に対してはPET検査での経過観察を推奨している。Ojiri[3]等，Anamaria[4]，後のMendenhall[5]等も放射線治療後のCTで残存が疑われる症例にのみ頸部郭清を行うことを提案している。ただし，これらの検討の対象としている疾患は中咽頭癌，下咽頭癌，喉頭癌をすべて含んだものであり，原発部位ごとの十分な検討はなされていないのが現状である。また，放射線療法を単独で施行した症例とCCRT症例では結果が異なることも考えられる。我々が以前に行った中咽頭癌・下咽頭癌症例に対するCCRT後に施行したPNDの検討では，比較的高率にviable cellの残存を認めた。また超音波検査や穿刺吸引細胞診を用いても転移残存リンパ節を評価することが困難であったため，積極的にPNDを施行すべきとの結論に至っている[6]。

今回の検討でも，中咽頭癌で50%，下咽頭癌では69%と，比較的高率にviable cellの残存が認められた。しかし，初回治療前の検索で転移が認められたレベル以外には病理組織学的にviable cellの残存や腫瘍瘢痕を認めなかった。

PNDの必要性については，CCRTの治療効果とあわせて症例毎に慎重に検討すべきであろう。また諸家の報告を参考にする場合は，その治療内容が各々の施設で施行している内容と乖離していないか十分に注意をするべきである。しかし一定以上の治療強度があれば，CCRT後のPNDでは治療前に把握されていたリンパ節転移陽性レベルを十分に郭清すればよいものと推測される。中咽頭癌ではレベルⅡ～Ⅲ，下咽頭癌ではレベルⅡ～Ⅳの領域を郭清範囲とし，転移があれば転移陽性領域を追加するのが妥当であろう。中咽頭癌症例に限定した検討ではあるが，Ilana[7]等の報告でも治療前にレベルⅠ，Ⅴに転移を認めていなければPNDの郭清範囲をⅡ～Ⅳに縮小しても頸部制御率を低下させないとあり，我々の検討結果を支持している。今後はさらに予後や合併症を含めてその妥当性を検討する必要があるものと思われた。

まとめ

1）中・下咽頭癌に対するCCRT後のPNDにおけるviable cell残存の有無を，リンパ節のレベル毎に検討した。

2）初回治療前の検索で転移が認められたレベル以外には病理組織学的にviable cellの残存や腫瘍瘢痕を認めなかった。

3）中咽頭癌ではレベルⅡ～Ⅲ，下咽頭癌ではレベルⅡ～Ⅳの領域を郭清し，転移があれば転移陽性レベルを追加するのが妥当であると思われた。

4）郭清範囲の縮小や省略の可能性については，さらに検討する必要があるものと思われた。

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