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Roles of Therapeutic Selective Neck Dissection in Multidisciplinary Treatment

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1. Introduction

In the treatment of head and neck squamous cell carcinoma (HNSCC), management of cervical lymph nodal metastases has a crucial impact on the prognosis of patients. The "radical neck dissection (RND)", which was proposed by Crile (Crile, 1906) in 1906, had long been played a role of standard treatment for neck metastases due to its high curability. However, during the last two to three decades, modified neck dissection (MND), also called as "functional neck dissection", which preserves non-lymphatic structures, has replaced the position of RND, because patients as well as surgeons have become more aware of the significance of the quality of life. In addition, it has become apparent that under current multimodality treatment protocols, MND can achieve improved functional results without compromising oncological outcomes, compared to the conventional RND (Ferlito et al., 2003). Of note, in this study, MND implies the comprehensive (I-V) ND that is generally termed as "modified radical neck dissection (MRND)", unless described otherwise. Moreover, the detailed studies on the patterns of potential neck metastases clearly demonstrated that the laryngeal and pharyngeal cancers seldom metastasize to the level I and V, while the oral cavity cancers to the level IV and V (Lindberg, 1972; Shah, 1990). These data have strongly encouraged the application of selective neck dissection (SND) that spares the dissection of at least one level in the treatment of clinically N0 neck as "elective" SND (ESND). It is now widely accepted that ESND can achieve similar regional control rates compared to comprehensive neck dissection (CND) (i.e., RND or MRND) in this N0 clinical setting with improved functional outcomes as summarized in a comprehensive review (Ferlito et al., 2006). Recent remarkable advancements in chemoradiation have further extended the application of SND to clinically N+ cases as "therapeutic" SND (TSND) instead of therapeutic CND (TCND). Efficacy of TSND performed either as an initial treatment or as a planed ND (PND) in the course of multidisciplinary treatments has been reported by an increasing number of studies (Ambrosch et al., 2001; Byers et al., 1999; Ferlito et al., 2009; Lohuis et al., 2004; Muzaffar, 2003; Patel et al., 2008; Shepard et al., 2010). Moreover, a recent study by Robins et. al., (Robbins et al., 2005) demonstrated that super selective (i.e., only two levels) neck dissection can achieve quite favorable outcomes, when performed as a PND after RADPLAT. In view of these observations, neck dissection (ND) has been recognized as a part of the multidisciplinary treatments composed of surgeries and concurrent chemoradiotherapy (CCR) in our institute. Consequently, we have applied MND as well as less extensive SN in both elective and therapeutic settings to patients with HNSCC, based on relatively simple principals. In this study, we have evaluated the efficacy of our application of ND.

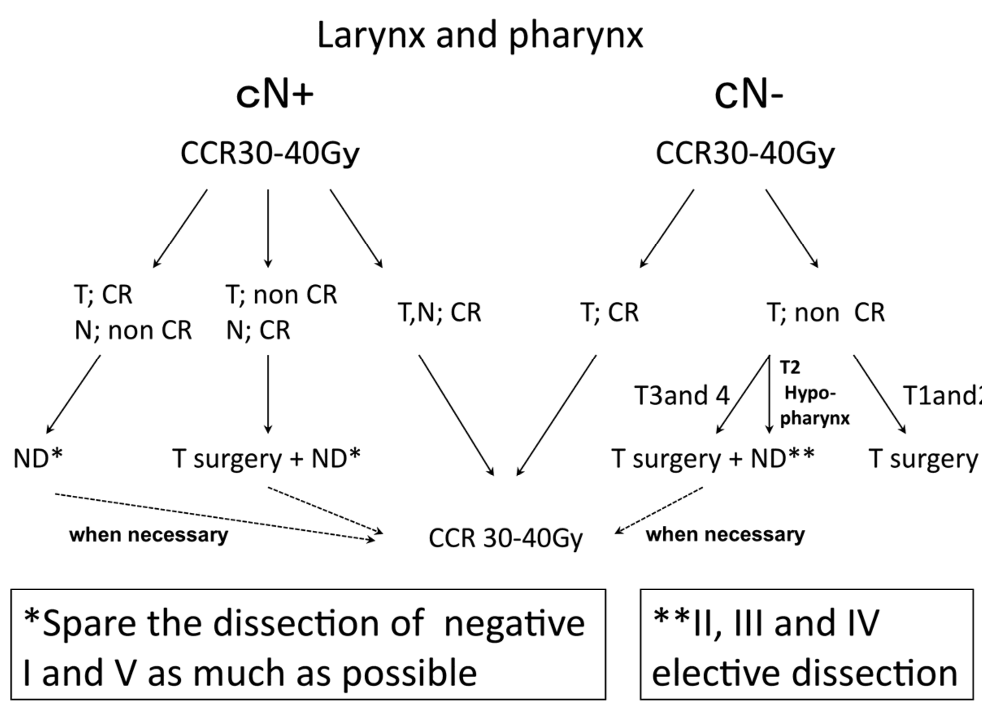

Fig. 1. Algorisms for the treatment of laryngeal and pharyngeal cancers

2. Patients and method

2.1 Eligibility and background of patients

Enrolled patients to this study were primary HNSCC patients who: (1) could have accomplished our protocol-based treatments with curative intent (Figs. 1 and 2), (2) underwent ND during primary treatment course and (3) had been followed more than 12 months. Based on a chart review of HNSCC patients who had been treated at the Department of Otolaryngology, and Head and Neck Surgery, Kyushu Koseinenkin Hospital, from June 2004 to June 2010, 66 subjects were selected. There were 55 male and 11 female. Their ages ranged from 34 to 80 with an average of 62.1. The primary tumors sites were: nasopharynx (n = 3), mesopharynx (n = 16), hypopharynx (n = 14), larynx (n = 11), oral cavity (n = 21), and primary unknown (n = 1). Clinical stage was determined using the 6th UICC TNM classification (2002). T stage was categorized as T1a (n = 1); T1 (n = 5); T2b (n = 1); T2 (n = 21); T3 (n = 20); T4a (n = 14); and T4b (n = 3), N stage as N0 (n = 14); N1 (n = 10); N2 (n = 2); N2a (n = 5); N2b (n = 26); N2c (n = 6); and N3 (n = 2), and clinical stage as I (n = 0); II (4); III (n = 15); Iva (n = 32); and IVb (n = 4). Of note, one primary unknown case was excluded from T and clinical stage classification. Thus, 63.6% (42/66) of patients displayed ≧N2 necks and 78.5% (51/66) of patients were categorized as having stage III-IV advanced HNSCCs. The median follow-up period was 34.1 months ranging from 7 - 85 months.

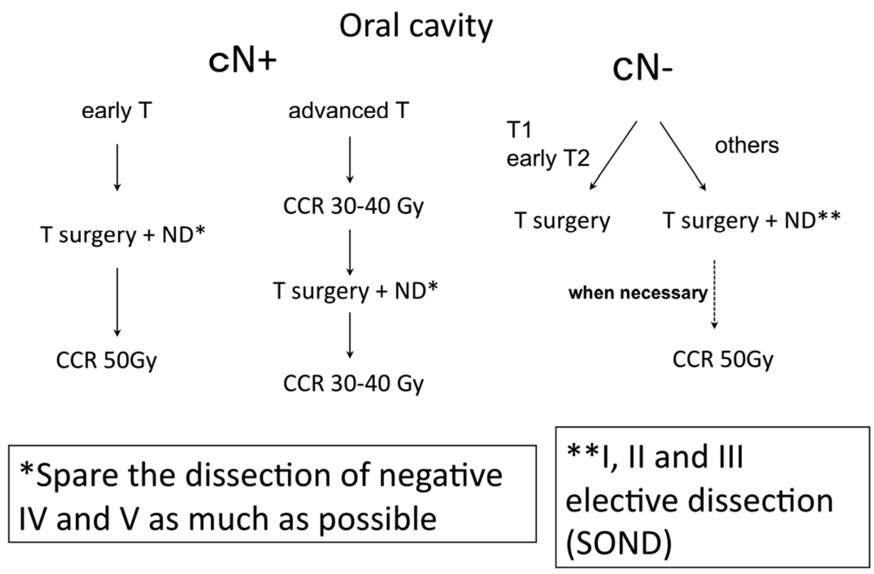

Fig. 2. Algorisms for the treatments of oral cavity carcinomas

2.2 Treatment protocol

All patients, expect for one primary unknown case, were treated with our treatment protocols shown in Figs. 1 and 2.
Briefly, tumors from the pharynx and larynx (Fig.1), and oral tumors with advanced T and N+ (Fig.2) were initially treated with 30-40 Gy of concurrent chemoradiotherapy (CCR) composed of S-1 (80-120mg/day, p.o.), Vitamin A (50.000 IU/day, i.m.) and external beam of irradiation (1.8-2.0 Gy/day), which we have termed "TAR therapy" (Kumamoto et al., 2002; Nakashima et al., 2005). Then further treatments course were determined according to the algorism demonstrated in Figs.1 and 2.
For oral cavity tumors with early T and N+ or any T and N0, surgery was adopted as an initial treatment modality and then additional CCR was administered when necessary. One primary unknown case underwent an initial ND and additional 50 Gy of CCR. In these protocols, ND has been considered as a part of multidisciplinary treatment, and therefore organ preserving ND and both elective and therapeutic SND have been employed as our standard option for neck metastases. Our basic policies for ND are as follows: (1) preserve the spinary accessory verve (XI), internal jugula vein (IJV) and sternocleidmastoid muscle (SCM) (of note, the SCM is sacrificed when primary tumor site is reconstructed with a pectoralis major myocutaneous flap), unless direct invasion of tumors is highly suspected, (2) in N+ cases, the dissection of positive N levels is mandatory, but omit the dissection of respective I and V for laryngeal and pharyngeal cancer and IV and V for oral cavity cancer (Figs. 1 and 2), considering the size, position, number and invasiveness of the positive N located in the adjacent levels, and (3) in N0 cases, we employ ESND: II, III, and IV dissection for laryngeal and pharyngeal cancer, and I, II, and III dissection for oral cavity cancer (i.e., SOND) (Figs. 1 and 2). These protocols are approved by the Hospital Review Board.

2.3 Neck dissection

2.3.1 RND

Fig.3 demonstrates the surgical view of RND for primary unknown bulky nodes and consequent cosmetic and functional results. Deformity of the dissected neck and shoulder-drop are prominent. He has severe difficulty in stretching up of the left arm.

Fig. 3. RND

2.3.2

Fig.4 displays the surgical view of MRND performed during a pull-through glossectomy. The SCM muscle was sacrificed for the reconstruction with a PMMC flap.

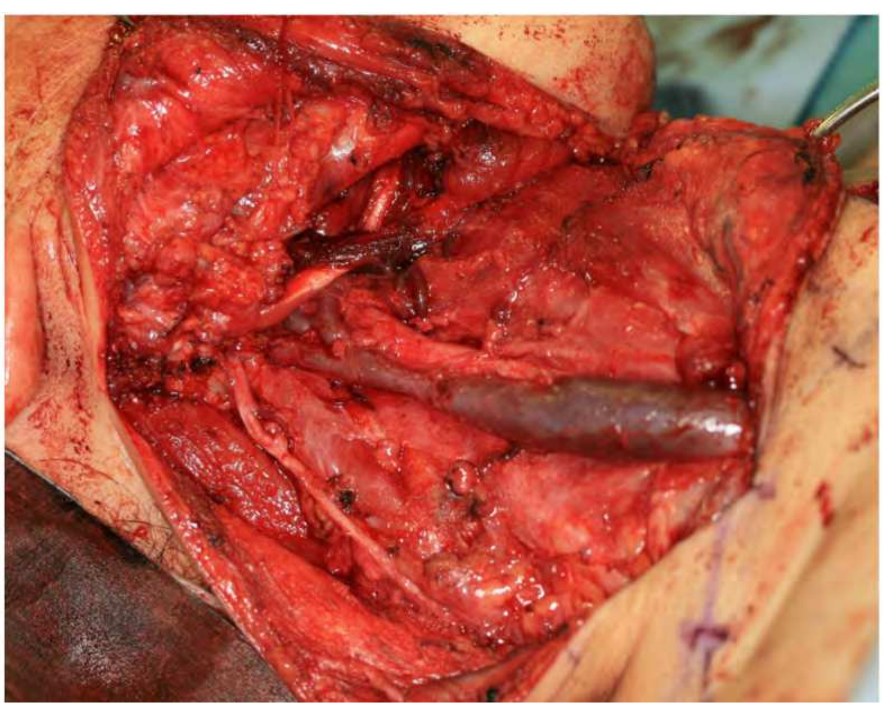

Fig. 4. MRND

2.3.3

Fig.5 displays the surgical view of TSND (II-IV) for mandibular preserving pull-through oropharyngectomy (Masuda et al., 2010). In addition to the XI nerve, SCM and IJV, the facial vein, the external jugular vein, the great auricular and the cervical nerves were preserved.

Fig.5. TSND

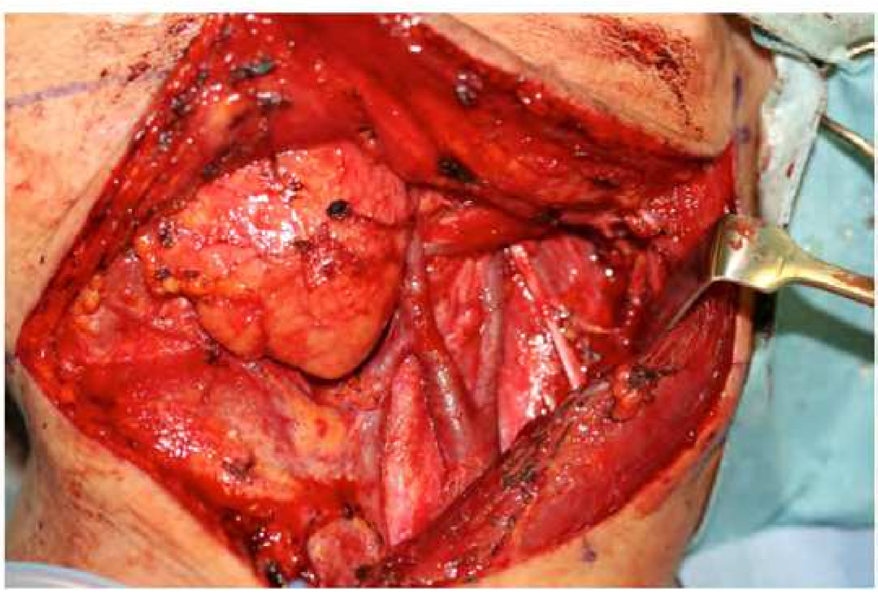

Fig. 6. SOND

2.3.4

Postoperative view of SOND (I-III) performed as an ESND (Fig.6). In this case, the submandibular gland, facial vein, external jugular vein and great auricular nerve were preserved, as well as the XI nerve, SCM and IJV

2.4 Treatment course

Under these protocol-based treatments, 66 patients received 78 NDs. According to the status of nodal metastases and the type of ND they received, 78 necks were divided into 4 groups (Fig.7). Among 15 N0 necks, Group1 (n = 12) underwent ESND, while Group 2 (n = 3) received CND (MRND). For 63 N+ necks, 36 TSNDs were administered to Group 3, while 27 TCNDs (20 MRNDs and 7 RNDs) to Group 4. Except for 3 cases in Group1 and 1 case (pN0) in the Group 3, CCR was administered to 94.9 % (74/78) of cases.

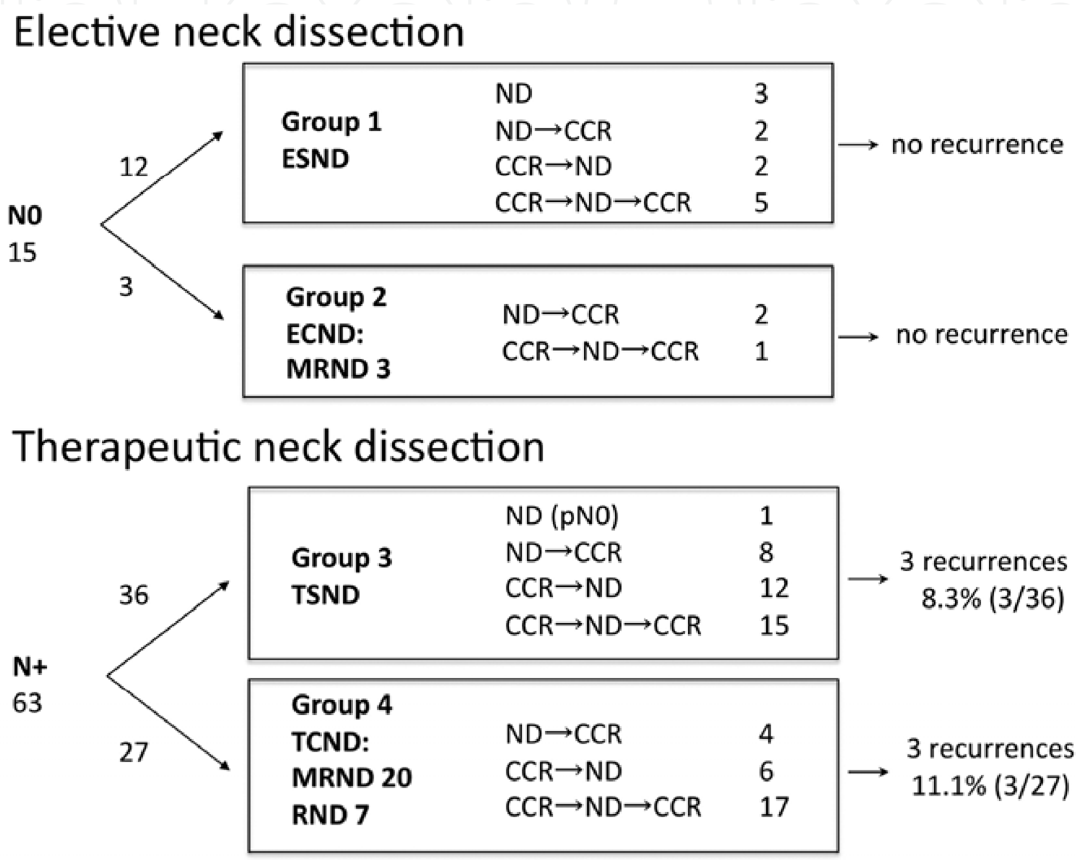

Fig. 7. Grouping of the 78 necks based on the status of nodal metastases and treatment courses

3. Results

3.1 Non-lymphatic structures and level preserved

Conventional RNDs were applied for 7 N+ cases, accounting for only 9% of all NDs. In more than 90% of cases, at least one of the XI nerve, SCM, or IJV was preserved. The detail with respect to organ preservation is shown in Table.1. The XI nerve and SCM were left intact in more than 80% of cases and the SCM in 55.1% of cases. The lowest preservation rate of the SCM among these three organs was due to its sacrifice for reconstruction by a PMMC flap. All the three XI nerve, SCM, and IJV were spared in approximately half (47.4%) cases.
In 21 necks with oral cavity cancer, the dissection of level III, IV and V was omitted at 9.5%, 33.3% and 66.7%, respectively. For 56 necks with laryngeal and pharyngeal cancer the preserving rates of respective I, IV and V were 50.1%, 14.0% and 49.1% (Table.2).
One patient with primary unknown neck metastases (N2b) was treated with RND (Fig. 3).

Preserved organ	Rate of preservation
Spinal accessory nerve	80.1% (63/78)
Sternocleidmastoid m.	55.1% (43/78)
Internal jugular vein	82.0% (64/78)
Two of three	78.2% (61/78)
All three	47.4% (37/78)

Table 1. Organ preservation rates

Tumor Site	Level preserved (%)				
	I	II	III	IV	V
Oral cavity (n = 21)	0	0	9.5	33.3	66.7
Larynx & pharynx (n = 56)	50.1	0	0	14.0	49.1

Table 2. Level preserved

3.2 Distribution of Clinical Stage in SND and CND

In Table 3, the clinical stages of dissected necks were categorized based on the type of neck dissection: SND or CND. A majority of cases in both groups belonged to the advanced stage: 93.5% in SND and 100% in CND. This difference was not statistically significant. A primary unknown case was excluded from this analysis.

	Type of ND										
	SND						CND				
	NO	N1	N2	N3	total		NO	N1	N2	N3	total
T1	0	0	3	0	3	T1	0	1	1	1	3
T2	3	4	10	0	17	T2	0	1	4	2	7
T3	4	1	8	0	13	T3	3	1	6	0	10
T4	5	3	6	0	14	T4	0	0	10	0	10
total	12	8	27	0	47		3	3	21	3	30
	Stage III : 9 (19%) Stage IV : 35 (74.5%)						Stage III : 6 (20%) Stage IV : 24 (80%)				

Table 3. Comparison of the clinical stages between SND and CND

3.3 Local control and survival

The 78 dissected necks developed 6 (6.8%) recurrences, which were observed in the cases that underwent therapeutic ND (i.e., Group 3 and Group 4) (Fig.7). The recurrence rate was

8.3%(3/35) in Group 3 with TSND and 11.1 % (3/27) in Group 4 with CND. All 6 recurrences occurred in the dissected levels. Extracapsular spread of dissected nodes was observed in 50% (3/6) of recurrent cases: 1 case in Group 3 and 2 cases in Group 4, and caused the death of the patient. The remaining three recurrences without extracapsular spread, 2 in Group 3 and 1 in Group 4, have been surgically salvaged so far. The cumulative regional control rates, disease specific survival rates and overall survival rates were plotted with the Kaplan-Meier method, comparing the results of SND to those of CND (Fig.8).

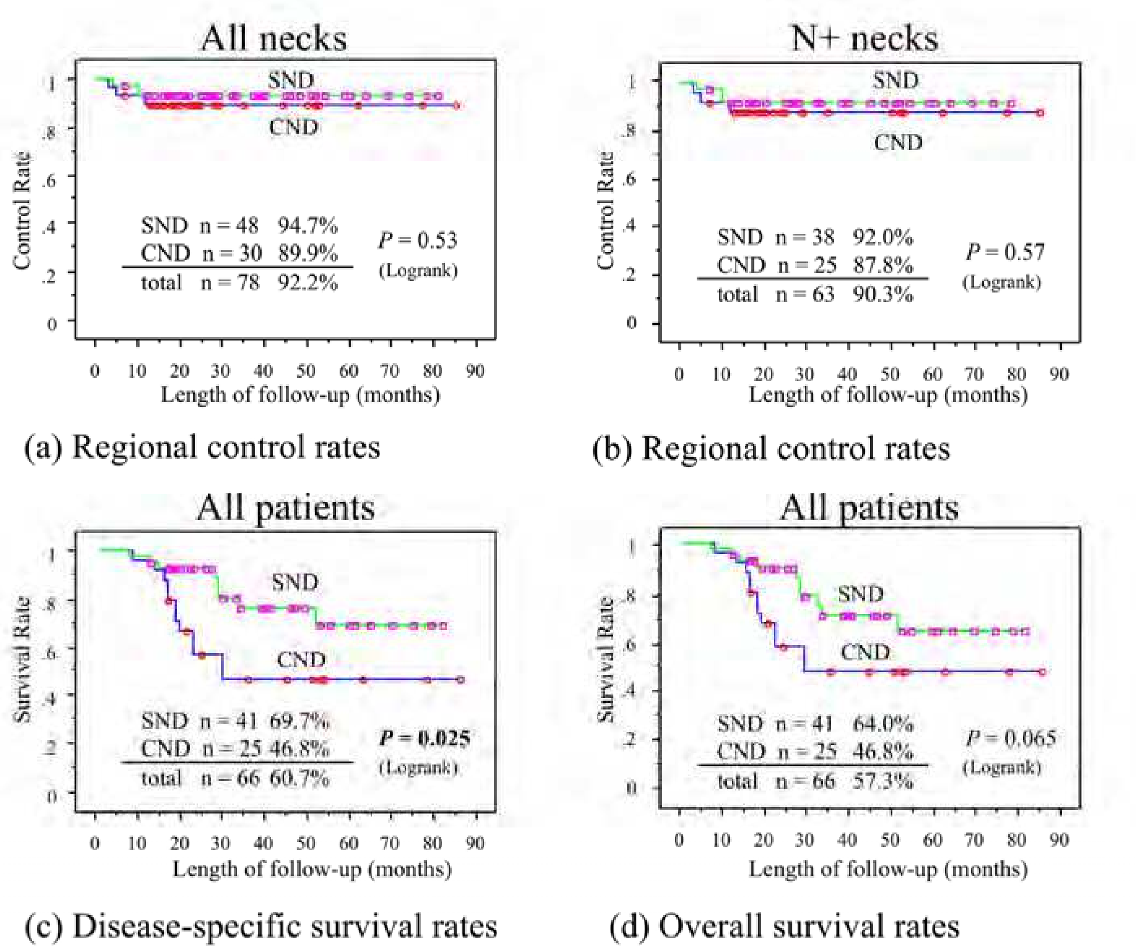

Fig. 8. The Kaplan-Meier plots for regional control and survival rates

In the overall (SND + CND) analysis, quite favorable regional control was obtained in the cohort of all necks (92.2%) (Fig. 8a) as well as in the cohort of N+ necks (90.3%) (Fig.4b). There was a tendency that the regional control rate of SND was higher than those of CND, thus SND yielded 94.7% in all necks and 89.9% in N+ necks, while CND 89.9% in all necks and 87.8% in N+ necks (Figs.8a and 8b). However, these differences were not statistically significant in the comparison studies by the Logrank test. The cumulative and over all disease specific survival rates were 60.7% and 57.3%, respectively (Figs. 8c and 8d). In the disease specific analyses, the SND group displayed significantly (*P* = 0.025) better prognosis (69.7%) than the CND group (46.8%)(Fig.8c). This tendency was also observed in the overall survival curves, but the difference between SND (64%) and CND (46.8%), was not statistically significant (*P* = 0.065) (Fig.8d).

3.4 Causes of deaths

In the present study, 22 deaths were observed. Twenty patients were died with causes related to the primary cancer: distant metastases, (n = 10), metastases to the Rouviere node (n = 2), primary tumor recurrence (n = 4), nodal metastases in the un-dissected neck (n = 2), and nodal metastases in the dissected neck (n = 3). The remaining two deaths were unrelated to the primary tumor: accident and pancreatic cancer. Consequently, regional failures in both dissected and un-dissected necks accounted for only 22.7 % (5/22) of deaths. Moreover, only 3 regional failures in the dissected necks were responsible for the deaths. More detail about regional failures of the dissected necks is described above.

4. Discussion

4.1 SND for N0 necks

The efficacy of SND for N0 necks as an elective ND has been confirmed by a solid body of evidence (Ferlito et al., 2003; Ferlito et al., 2006). Thus, it is not surprising that in the present study there were no recurrences in Group 1 undergoing ESND as well as in Group2 undergoing ECND (Fig.3). This high control rate might also be attributable to the fact that as many as 75 % (9/12) of necks in Group 1 received CCR. Thus, application of ESND for N0 necks, especially when they are treated with multidisciplinary treatment, seems to be adequate for selected patients.

4.2 TSND in multidiciplinary treatment

In accordance with the trend of multidisciplinary treatment, TSND has gained a wider acceptance in the treatment of HNSCCs. In general, TSND has been applied under two different lines of treatment regimens: (1) as an initial surgery followed by radiotherapy (Ambrosch et al., 2001; Byers et al., 1999; Lohuis et al., 2004; Muzaffar, 2003; Patel et al., 2008; Shepard et al., 2010), or (2) as a planned ND following CCR (Ferlito et al., 2009). In the former regimen, the indication of adjuvant radiotherapy was not uniform and in some studies it was mandatory but in others it was given to selected patients with risks including extracapusular spread, multiple pathological nodes and advanced T stage. However, irrespective of the application pattern of adjuvant radiotherapy, the regional recurrence rates of SND were 3-13% and more importantly theses figures were equivocal to or lower than those of CND in the studies that compared these two cohorts. The latter regimen apparently reflects the recent paradigm shift of the treatment for advanced HNSCCs. Thus, the current mainstay is induction CCR - in particular, dose-intensified - followed by a planned ND (PND). It was clearly demonstrated in a recent comprehensive review (Ferlito et al., 2009) that by means of SND or super SND, equivalent and safer results can be obtained compared to more extensive ND, although the indication of PND to cases that displayed complete response after CCR is now raising a hot debate.

In view of these two lines of regimens, our treatments protocols seem to be unique and lie at the intermediate between them. Thus, except for the early stage oral cancers, for which surgery has been reported to be more efficient than external irradiation, CCR is administered first. Then, at 30-40 Gy of CCR, we screen responders who can proceed to organ preservation arm; a screening method we have termed “chemoradioselection”. Since 1972, we have used this method for approximately 40 years for the treatments of HNSCC, achieving high organ preservation and survival rates especially in laryngeal cancer (Kumamoto et al., 2002). Similar concept of "chemoselection" has been recently proposed by the group of University of Michigan (Urba et al., 2006; Worden et al., 2008; Worden et al., 2009). They demonstrated that those who display favorable responses to induction chemotherapy tend to be cured by additional chemoradiotherapy without surgical intervention, facilitating organ preservation.

Considering the above mentioned trend for less extensive ND in the context of our treatment concept, we have applied organ preserving MND and SND in both elective and therapeutic clinical settings for the treatment of HNSCC. The aim of this study was to evaluate the efficacy of our application of ND, in particular, that of TSND. In both clinical settings, quite favorable regional control rates (84.7-94.7%) were obtained (Figs. 4a and 4b). These figures are similar to or better than those reported in the studies mentioned above. Thus, it is apparent that high organ preservation rates in the present study (Table 1) do not compromise regional control. Furthermore, it is also demonstrated that our indication of ND determined in the algorism-based protocols (Fig. 1 and 2) is quite acceptable. In conclusion, when employed under a definite principal, TSND is a reliable alternative to MRND and RND in multidisciplinary treatment.

In addition to the high regional control rates, patients in the present study displayed relatively favorable disease-specific (60.7%) and overall (57.3%) survival (Figs. 4c and 4d), although 77 % of patients had advanced stage. This is, at least in part, due to the high regional control rates observed in both SND and CND cohort, thus only 5 patients died with regional failure. However, in both disease-specific and overall survival analyses, the CND cohort displayed apparently poor prognosis, reflecting the aggressiveness of the initial tumor status of this population that led to deaths unrelated to the regional failure (e.g., distant metastases, the Rouviere nodal metastases and primary tumor recurrences). This finding might imply the limit of our treatment protocol. However, considering that the survival rates of this study is favorable even compared to those obtained by the recent dose-intensified types of treatment protocols summarized in a recent review (Ferlito et al., 2009), it seems to be quite challenging to develop a practical countermeasure to improve the prognosis of this population with highly aggressive tumors.

5. Conclusions

Organ preserving SND in both elective and therapeutic clinical settings is a quite reliable alternative to more aggressive ND (i.e., RND and MRND), when properly applied in multidisciplinary treatment.

6. Acknowledgement

This study was supported in part by fund from Grants-in-Aid for Scientific Research (C): 21592195 to Muneyuki Masuda

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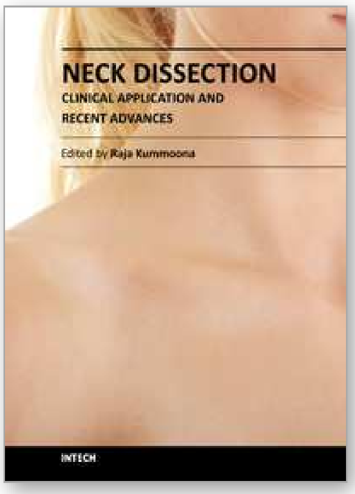

Neck Dissection - Clinical Application and Recent Advances
Edited by Prof. Raja Kummoona

ISBN 978-953-51-0104-8
Hard cover, 164 pages
Publisher InTech
Published online 22, February, 2012
Published in print edition February, 2012

Neck Dissection - Clinical Application and Recent Advances is a leading book in neck surgery and represents the recent work and experiences of a number of top international scientists. The book covers all techniques of neck dissection and the most recent advances in neck dissection by advocating better access to all techniques of neck dissection; e.g. Robotic surgery (de Venice) system, a technique for detection of lymph node metastasis by ultra sonography and CT scan, and a technique of therapeutic selective neck dissection in multidisciplinary treatment. This book is essential to any surgeon specializing or practicing neck surgery, including Head Neck Surgeons, Maxillofacial Surgeons, ENT Surgeons, Plastic and Reconstructive Surgeons, Craniofacial Surgeons and also to all postgraduate Medical & Dental candidates in the field.