

Salvage Neck Dissection after Chemoradiation in Head and Neck Cancer: Practice and Pitfalls

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ABSTRACT

Locally advanced head and neck cancers are usually treated with concurrent chemoradiation. The residual nodes after chemoradiation in such patients are a common scenario, but the further investigation and treatment options in form of neck dissection are still not very clear. This review focuses on the current state of available evidence in literature for management of such patients and directs for the future development to fill the lacunae.

Keywords: Radiotherapy, Hypopharyngeal cancer, Oral cancer, Larynx, Chemoradiotherapy.

How to cite this article: Agarwal J, Kundu S, Krishnatry R, Gupta T, Murthy V, Budrukkar A, Laskar SG. Salvage Neck Dissection after Chemoradiation in Head and Neck Cancer: Practice and Pitfalls. *Int J Head and Neck Surg* 2012;3(1): 15-21.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Concurrent chemoradiation therapy (CRT) is an accepted primary treatment for locally advanced head and neck cancers. Although CRT often provides excellent local control, its efficacy in treating advanced regional disease (nodes) remains controversial. Current CRT protocols include treatment of nodal metastases in the neck, but there are a lot of discrepancies in recommendation for the residual nodes post-CRT. This includes the controversy of choice of investigation, timing of assessment, type and timing of neck dissection (ND) and case selection criteria. Also, there is scanty information in literature regarding management of complete clinical response in patients of advanced regional disease (N2 or N3). In this review, we present the concise evidence to date in literature for surgical management of neck nodes in radically treated head and neck cancer patients with CRT.

Neck Nodes are Important Prognostic Factor affecting Survival

The primary justifications for posttreatment ND in radically treated CRT patients are; the 25% chance of residual neck disease, the challenge of accurate clinical follow-up in patients with postradiotherapy neck fibrosis, and the poor outcomes in salvage neck surgery.¹ It has been reported

that any node-positive disease at diagnosis can lead to 5-year survival rates of less than 50%.² Brizel et al demonstrated a decreased rate of neck control by 35% in patients with N2 or greater regional disease who received CRT without ND as compared to ND patients.³ When occult metastases are present, overall survival drops to levels found in patients who present with node-positive necks at diagnosis, irrespective of the primary treatment modality employed.⁴ Failure in the neck after definitive neck treatment offers a distinctively poorer prognosis than local recurrences.⁵ In a tumor registry based study by Deschamps et al, out of 1291 patients of head and neck cancer treated between 1998 and 2007 there were 224 recurrences of which 47 isolated neck recurrences. Twenty-one percent of isolated neck recurrence patients had regional disease (N+) at initial presentation. Median survival and 5-year survival was 14.7 months and 5% for isolated neck recurrences than 40.1 months and 15% for others.⁶

Role of Imaging in detecting Residual/Recurrent Disease

The ideal investigation to ascertain the residual disease and decide for further treatment post-CRT is still not known. There have been discrepancies between findings on imaging studies and the presence of pathologic residual carcinoma in the neck adding dilemma to the decision of surgery vs observation. The key reason for this difference in different retrospective studies is not just in the final outcomes but probably in the timing of these investigations.^{7,8} Timing has different meaning for different investigations, ranging from viability and clonogenic capacity of the tumor cells still in those nodes (USS FNAC, PET) if done earlier than the time needed for regression, the morphological regression of these nodes (clinical, CT, USS or MRI), resolution of acute inflammation post-CRT (PET-CT), undue delay in surgery if we wait too long for investigations.⁹⁻¹¹ Also an important issue that becomes critical in most developing countries is the availability and the cost. So there cannot be the best investigation of choice suggested for all.

What can be suggested at this juncture is a clinical assessment at 8 weeks post-CRT, when the acute effects of treatment have subsided and before the chronic side-effects set in. When physical examination of the neck shows no

cervical adenopathy, for initial N1 and N2 disease observation with close follow-up may be suitable. When the findings at clinical examination are ambiguous, or if N3 node was present and there is clinical complete response is present; PET-CT (12 weeks), CT or MRI (8-12 weeks), USS neck can be planned in order of preference. If clinically suspected residual node after chemoradiation then its better to go ahead with planned ND. The investigations like CT, MRI, PET-CT or USS can help in identifying the involved levels of the neck to decide for extent of ND.^{12,13}

Is Planned ND Necessary after Initial CRT?

An early ND after residual disease in post-CRT (4-12 weeks) has shown several distinct advantages of improved regional control and survival. But the benefit of surgery in patients with a complete clinical response after CRT has been difficult to show; also most retrospective single-institution reviews are limited by inadequate statistical power to detect a survival advantage for this subset of patients.^{14,15} Another facet which has been rarely discussed is that the presence of pathologic residual carcinoma in the ND specimen has been associated with an increased risk of local and regional recurrence as well as distant failure.

The morbidity of a potentially unneeded procedure cannot be ignored because if there is no residual disease present these patients can be easily followed-up avoiding surgery. But if wrong patient is selected for observation it can lead to persistence or progression of disease in the neck necessitating salvage ND, which has been associated with an increased frequency and severity of postsurgical complications. A 'window' between acute and chronic CRT injury 4 to 12 weeks after radiation has been described to minimize the surgery-related complications.¹⁹

At this juncture, it is important to revisit the frequency of pathologic residual carcinoma in ND specimens which ranges from 20 and 68% and is affected by many factors including pretreatment nodal stage and bulk, radiation dose and technique, the use of chemotherapy, the timing and extent of ND, and most importantly clinical response to CRT or patient selection.¹⁶⁻¹⁹ Most authors prefer the planned dissection in all patients with evidence of clinical or radiological evidence of residual disease in neck, while prophylactic ND after complete response is done in N3 and rarely for N2 or N1 disease. Usually patients with complete response both clinically and radiologically are preferred for close observation especially with initial N2 or N1 nodes.

Types of ND—Which is the Optimum?

Radical neck dissection (RND) has been the standard treatment for cervical nodal metastases since it was first

described by Crile in 1906. It is a safe and reliable method of addressing the lymph nodes. Although RND is an excellent technique, it is nonetheless associated with substantial morbidity. The Committee of Head and Neck Surgery and Oncology and the American Academy of Otolaryngology/Head and Neck Surgery have revised the terminology and classification of neck dissection.²⁰

Radical neck dissection (RND): Resection of cervical lymph nodes from all five levels along with sternocleidomastoid muscle (SCM), internal jugular vein (IJV) and spinal accessory nerve (SAN).

Modified radical neck dissection (MRND): Modification of RND with preservation of one or more nonlymphatic structures.

Selective neck dissection (SND): Modification of RND with preservation of one or more lymph node groups, which are removed in RND.

Extended radical neck dissection (ERND): Removal of additional lymph nodes (occipital or parotid nodes) or nonlymphatic structures relative to a RND.

In a review by the Committee of Head and Neck Surgery and Oncology and the American Academy of Otolaryngology/Head and Neck Surgery, the committee noted that there was a worldwide desire to maintain their previous classification but felt that minor modifications had to be amended to keep with the current philosophy of cervical nodal metastases.²¹ As such, modified radical neck dissection (MRND) was divided into:

- i. **MRND type I:** Resection of SCM, IJV and all five levels of cervical lymph nodes (preservation of SAN)
- ii. **MRND type II:** Resection of SCM and all five levels of cervical lymph nodes (preservation of SAN and IJV)
- iii. **MRND type III:** Resection of all five levels of cervical lymph nodes (preservation of SAN, IJV and SCM).

Similarly, selective neck dissection (SND) was also divided according to the levels of lymph node dissected:

- i. **Supraomohyoid neck dissection (SOHND):** Resection of all lymph node levels from I to III.
- ii. **Lateral neck dissection (LND):** Resection of all lymph node levels from II to IV.
- iii. **Posterolateral neck dissection (PLND):** Resection of all lymph node levels from II to V.

The gold standard procedure used till date for treatment of residual or recurrent cervical lymph nodes following CRT is radical neck dissection (RND) and modified radical neck dissection (MRND). However, there is still considerable debate regarding the use of selective neck dissection (SND) in cases with advanced nodal disease. Traynor et al suggested that the use of SND could be extended to N2B

and N2C disease, in the absence of massive lymphadenopathy, nodal fixation, gross extracapsular spread (ECS) and a history of previous neck surgery.²² Considering the morbidities associated with the use of more comprehensive neck dissections in the postchemoradiation setting, a group of researchers are considering whether lymph node dissection can be confined to 1 or 2 contiguous neck node levels when there is a single positive neck node level (N1 or N2a). The term 'superselective neck dissection (SSND)' has come into vogue but it should be properly tested in a properly conducted randomized control trial before it comes into practice.

Superselective ND (SSND)

Superselective ND is defined as the removal of all fibrofatty tissue contents, including lymph nodes, along the defined boundaries of 1 or 2 contiguous neck node levels.¹⁶ CRT has become an important treatment option for locally advanced head and neck cancer. When compared with radiation therapy alone, the results have shown significant improvement in locoregional disease control and some modest improvement in overall survival.²³ The combination of chemotherapy and radiation therapy administered concurrently appears to be more potent than sequential CRT. Despite the success of this approach, there continues to be a debate on how to manage the associated nodal disease. The common approach used by the head and neck surgeons is to perform surgical salvage in the manner that has been well accepted and based on historical experience with patients that were treated with definitive radiation therapy. Based on this framework, it is a commonly held dictum that persistent or recurrent nodal disease should be managed with surgical procedures that are well encompassing and radical, as opposed to those that specifically address the levels of neck that are at greatest risk. The paradigm shift of CRT over radiation therapy alone brings into question the conventional types of ND procedures. Because the majority of lymph nodal disease is likely to be sterilized with the potent combination of chemotherapy and radiotherapy, it may be feasible to use ancillary ND procedures that are less extensive and result in reduced morbidity. Most patients who have persistent nodal metastases after CRT have limited positive disease that is confined to levels of high risk. Lymph nodes occupying neck levels that had no pretreatment evidence of disease involvement and that remain clinically negative after CRT rarely harbor occult metastases. Under these circumstances, it is unnecessary to remove such low-risk neck node levels when performing ND for patients with residual clinically positive disease confined to 2 or fewer neck node levels.

Robbins et al performed a prospective study to evaluate the efficacy of selective and SSND for patients with bulky or residual nodal metastases treated with concomitant CRT. Among the total group of 240 patients, 106 NDs were performed on 84 patients who had bulky nodal disease. With a median follow-up of 58 months (range 12-96 months), regional failure occurred in two (17%) of the 12 patients who had modified radical ND, three (65%) of the 65 who had selective ND, none of the seven patients who had superselective ND and six (4%) of the 156 patients who had no ND. The rates of overall survival and distant metastases were not significantly different among the three ND subsets.¹⁶

In another study performed by the same group of Robbins et al, they evaluated 177 node positive patients of head and neck cancer. Out of them, 81 had partial response after CRT and 73 had residual adenopathy involving only one neck node level. Within this subset, 54 patients (57 heminecks) subsequently underwent a salvage ND, for which comparisons were made between the restaging evidence of residual adenopathy and the pathologic findings that were specific for each neck level. Only two of the 54 patients had evidence of pathologic disease extending beyond the single neck level: One had disease in a contiguous neck level, and the other had disease in a noncontiguous level. The use of superselective ND with removal of only two contiguous neck levels would have encompassed known disease in all but one patient. Hence, they concluded that superselective ND is feasible after CRT has been administered to patients with persistent nodal disease that is confined to one level.²⁴

ND after CRT for advanced head and neck cancer with associated bulky nodal disease is not without risks related to wound healing and chronic soft-tissue fibrosis. Dissection of all neck levels was reported to increase the incidence of spinal accessory nerve dysfunction and have a negative impact on quality of life.²⁵ The concomitant use of CRT is a potentially lethal weapon that is likely to sterilize most of the metastatic lymph nodes in the neck. Therefore, in an attempt to treat the residual adenopathy in the neck treated with CRT and to reduce the postoperative complications, probably, superselective ND (removal of ≤ 2 contiguous neck node levels) would be appropriate. For clinically overt nodal disease after CRT, ND is essential. However, for clinically negative nodal disease before CRT, one can argue that occult nodal disease present in these areas before CRT has already been sterilized by CRT.²⁶

The advantage of surgical conservation approach used in this group of patients with residual nodal disease after primary CRT relates to minimizing the extent of surgical

field thereby reducing the chances of postoperative soft tissue fibrosis. Fibrosis remains a significant problem for patients who require surgery in this setting because of its impact on swallowing, mastication, and range of motion of neck movements. Superselective NDs, however, can be performed with much smaller incisions, and the dissections are limited to two levels. Patients who have undergone a superselective ND typically recover without developing extensive soft tissue fibrosis. The majorities of patients undergoes the procedure and are discharged from the hospital on the same day. Last but not the least, there is still no randomized clinical trial addressing the effectiveness of SSND in salvage setting with persistent neck node in one level following CRT. A properly conducted randomized clinical trial may change the treatment outlook in this subset of patients.

Elective ND in Locally Recurrent Setting in Initial N0 Neck

The optimal management of node-negative neck during salvage surgery of locally recurrent head and neck cancer after initial CRT is not known. Because the neck can be seeded during local recurrence, it is believed that there is a high likelihood of regional metastatic disease.²⁷ Therefore, it is a common practice to include ND during salvage surgery for locally recurrent head and neck cancer. ND after radiation has been associated with decreased quality of life, increased operative time and increased chances of complications. The influence of elective ND on complications cannot be easily dismissed. ND after RT was shown to be an independent prognostic factor for increased severe late toxicity in a multivariate analysis of 230 patients included in three prospective trials, radiation therapy oncology group (RTOG) 91-11, RTOG 97-03 and RTOG 99-14.²⁸ Parsons et al reported a high rate of 23% for moderate/severe complications (fistula, tube feeding, and wound breakdown requiring graft or resulting in carotid exposure) after salvage with and without ND for recurrent SCCA of the supraglottic larynx, but the influence of ND on toxicity was not analyzed in this study.²⁹ After radiation, changes in the lymphatic tissues, including decrease in the nodal size and the caliber of the lymphatic vessels have been observed. It is also seen that after irradiation with more than 40 Gy dose, lymphatic structures become hyalinized and fibrosed.³⁰ These changes may act as a barrier for lymphatic dissemination for locally recurrent tumors after initial chemoradiation.

Yao et al published their results of 63 patients of locally recurrent laryngeal cancer (supraglottic and true glottic) treated initially with radiation. Out of these, 43 patients underwent ND in addition to local salvage surgery and

20 patients underwent salvage local surgery only with observation of the neck. Five (12%) out of 43 patients had pathologically positive neck node after dissection. There was no difference in 5-year overall survival between the neck dissected and observed groups.³¹

Dagan et al did a retrospective review of 57 patients of locally recurrent head and neck squamous cell carcinoma who were initially treated with elective nodal irradiation (ENI). Forty patients underwent ND and 17 patients had neck observation only. In the dissected group, the 5-year local control, regional control, cause-specific survival, and overall survival rates were 71, 87, 60 and 45% respectively, compared to 82, 94, 92 and 56 respectively, for the observed group. Toxicity was more likely with dissection. There were two postoperative deaths in the neck-dissection group. One patient experienced a perioperative myocardial infarction, chronic aspiration pneumonia, and died of aspiration and sepsis 6 months after salvage. The other patient had postoperative wound complications including a pharyngocutaneous fistula, carotid exposure, and died without being discharged from the hospital 1 month after attempted salvage. In the pooled analysis of total of 230 patients, the overall pathologic positive rate of neck-dissection specimens was 9.6%; the compiled data showed no improvement in outcomes when salvage included ND. They concluded that routine elective ND should not be included during salvage surgery for locally recurrent head and neck cancer, if initial radiotherapy includes elective nodal irradiation.³²

There is a low rate of occult regional nodal metastases (~10%), no improvement of outcomes after adding elective ND to the primary salvage procedure and an increased rate of complications with elective neck node dissection. Given the high negative predictive value for regional metastatic disease, all recurrent head and neck cancers are restaged with contrast-enhanced CT. If there is no suspicion for regional disease, it is justifiable to exclude elective ND as part of the salvage procedure in most cases. It remains unknown whether this practice is applicable in other settings, such as in patients who were initially treated for node-positive disease and are salvaged for isolated recurrences or in patients undergoing salvage for a second primary head and neck cancer. In these settings, neck should be managed with elective ND until data is available showing that a less aggressive approach is equally effective.

Neck Recurrence following Radical ND: Second ND

Second (radical) ND implies salvage radical surgery to the neck, with curative intent, with or without adjuvant therapy. Adjuvant external beam radiation after ND may be given, if there are multiple positive lymph nodes or perinodal

extension of disease. However, this treatment philosophy is more valid when there is occult neck node metastases rather than frank neck node disease. Most centers report a low rate of recurrence in the neck following ND (~14%). Although this appears low, the fact that patients with neck node metastases have a much reduced survival compared with those without merely demonstrates the tumor's capacity to spread outside.

There are a number of theories regarding the cause of recurrence in the neck following radical ND. An aggressive histological behavior is correlated with the extent of both primary regional disease and recurrent regional disease.³³ A number of patients will have micrometastases present either in the tissues of the neck or within lymph nodes that have been missed during the original radical ND, and these have been implicated as the source of a recurrence in a number of patients.³⁴

In a series published by Jones et al, most patients who had primary radical ND suffered no recurrence in the neck, with a cure rate of 56%, significantly higher than usually quoted. Of those who had a recurrence and were treated with second ND, 31% were cured. Of those that had no curative treatment to their neck, there were no long-term survivors and a median survival of 7 months only.³⁵ The literature dealing with recurrent regional disease is not extensive, perhaps because it has been considered an unrewarding area of study. Nevertheless, figures show that a third of patients can be saved if they are suitable for radical retreatment. As lymph node metastases and particularly recurrent lymph node metastases are the most important prognostic factor in head and neck cancer, recurrent regional disease is worthy of more study.

Complications of ND after Initial CRT

As with any surgical procedure, neck dissection is associated with several potential complications that can be prevented by meticulous surgery and careful follow-up. Although many of these complications are rare in the hands of an experienced surgeon, some are nonetheless unavoidable. Trauma to the internal jugular vein may lead to intraoperative bleeding that may be difficult to control. Although rare, the possibility of an air embolus following trauma to the IJV should be borne in mind. Cardiac arrhythmias can also occur during neck surgery. Manipulation of the carotid bulb during dissection of the internal jugular vein can lead to the arrhythmias that can be life-threatening. Carotid artery rupture is associated with 35 to 50% mortality. Disruption of the sympathetic chain may also result from neck dissection, following dissection of the carotid sheath, leading to Horner's syndrome. Chylous fistula occurs in 1 to 2% of neck dissections. If a chylous leak is detected intraopera-

tively, every effort must be made to find the source and suture the opening. Fluid collection under the skin flaps can be prevented by using suction drainage.

Late complications are most severe when neck dissection is carried out after CRT. The formation of a neuroma may considerably affect the day to day life of the patient. In such cases, it is important to ascertain that any lump in the neck is not a sign of recurrent disease. Similarly, chronic shoulder pain may impair the daily activities of the patient. Competent physiotherapy may help to improve the condition of the patient. Fibrosis and neck stiffness is the most morbid complication after neck dissection in a post-CRT patient. The fibrosis associated with previous radiotherapy makes it more morbid for the patient. The surgeon should be aptly conscious regarding the complications and multidisciplinary approach involving physiotherapist should be involved for vigorous neck exercises and physiotherapy.

Quality of Life Issues

The real issue behind this discussion to justify observation or surgery in postchemoradiation patients has been very scantily discussed in literature. Although the physical complications due to various NDs have been discussed in detail in literature, the quality of life issues have been ignored for long. There is only one study addressing this issue till date. Amy et al prospectively analyzed quality of life issues in 103 oropharyngeal carcinoma patients with stage IV at two tertiary centers undergoing CRT alone in 64 and CRT followed by ND in 38 patients. They collected information using SF-36 and HNQOL using self-administered health survey at pretreatment and 1 year post-treatment. It was seen that only the pain index of the SF-36 was significantly more in patients undergoing ND after CRT, while all other QOL scores were similar in two groups. There were many inherent deficiencies in this study, but to name a few were small size, unequal number of patients in two groups, heterogeneities in the groups and short follow-up.³⁶

Beyond Post-CRT ND

It is understood that patients with pathologically positive lymph nodes at ND post-CRT are at high risk for local, regional and systemic disease recurrence.³⁷ The theories range from radiation and chemotherapy resistant clones, pre-treatment dissemination of micrometastasis in neck or distant sites, pathological risk factors in dissected nodes. The proof of theories is still largely unavailable in literature. It is proposed that identification of the pathological risk factors in neck may help in planning the future treatment beyond, but the pathological assessment of these nodes is

limited due to inability to distinguish between squamous carcinoma cells initiating apoptosis vs those undergoing repopulation and may need further markers identification. Also it is known that level V involvement in ND is associated with an increased risk of disease recurrence with improvement in neck control but no significant impact on survival.^{16,17} Few factors need further evaluation like: More than single node involved, macroscopic or microscopic involvement, ECS or soft tissue involvement. Also this may be taken as an opportunity to introduce newer therapies like hyperthermia, metronomic chemotherapy, and targeted agents in such patients after identification of appropriate risk factors.

CONCLUSION

So, it is important to understand for both the treating oncologist team and patient for the necessity, ways and implications of addressing neck nodes in patients of locally advanced head and neck cancers. It may be a critical decision between observation and neck dissection or morbidity and mortality. Both clinical and radiological responses are necessary to be assessed together before appropriate decision in time. PET-CT has increasing role in coming future.

Early neck dissection of patients at a high risk of regional recurrence provides an opportunity for neck control and survival. Limited neck dissection may be sufficient and can be considered for some patients. It urgently needs further trials on this issue with prospective large set of patients to move beyond consensus statements of reviews of institutional practices and retrospective data (Table 1) to enraged facts. There is also a lacuna of evidence of identification of high-risk features post-ND and methods to address them.

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Table 1: Model of planned ND strategy

	<i>Investigation of choice</i>	<i>Timing</i>	<i>Treatment</i>	<i>Timing</i>
Initial N2 disease	Clinical examination with 1. PET-CT 2. CT or MRI 3. USS neck	8-12 weeks	1. If negative, observe only 2. If borderline, observe or selective neck dissection 3. If residual disease present, selective neck dissection or comprehensive neck dissection	8-12 weeks
Initial N3 disease	Clinical examination with 1. PET-CT 2. CT or MRI 3. USS neck	8-12 weeks	1. If negative, observe or selective neck dissection 2. If borderline, observe or selective neck dissection 3. If residual disease present, selective neck dissection or comprehensive neck	8-12 weeks
Isolated neck recurrence	Clinical examination with 1. PET-CT 2. CT or MRI 3. USS neck Guided FNAC, if required	NA	Comprehensive neck dissection	NA

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