Neck Dissection Followed by Definitive Radiotherapy for Small Upper Aerodigestive Tract Squamous Cell Carcinoma, with Advanced Neck Disease: An Alternative Treatment Strategy

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Abstract Treatment options for patients with small upper aerodigestive tracts squamous cell carcinoma (T1, T2) with advanced neck disease (N2, N3) is a topic that generates controversy in terms of therapeutic strategies. We present the retrospective analysis of 109 patients treated, between 1991 and 2008, by “Neck dissection first approach” for N2, N3 neck node, followed by external beam radiotherapy (RT) with or without chemotherapy for the operated neck and the primary, deemed radiocurable. 94 patients completed the planned treatment and formed the material for this study. The primary (tumor) stage was as follows: T1 (29) and T2 (65) commonly arising from oropharynx; the neck nodes were predominantly N2a ($n = 54$), followed by N2b ($n = 26$) and N3 ($n = 14$) disease. Complete nodal clearance was achieved in 89 patients, with no major post operative complications. With a median follow up of 24 months disease free survival of 70% and overall survival of 61% at 5 years. Recurrence at primary site was noted predominantly with pyriform fossa tumors ($n = 8$),

followed by base of tongue ($n = 5$) and were T2 lesions. Failure in the neck was seen in predominantly N3 nodes, R1 resection and failure to comply with adjuvant treatment. Neck dissection first approach is a valid treatment option that allows a good control of the disease in the neck, where it often fails if only RT is administered, along with preserving the pharyngolaryngeal function. Care should be exercised so that there should be no delay in initiating the RT following surgery.

Keywords UADT cancer · Neck nodes · Neck dissection · Radiotherapy

Introduction

Small (T₁, T₂) upper aerodigestive tract (UADT) squamous cell carcinoma (SCC) with large neck nodes (N₂, N₃) is not an uncommon clinical entity. They represent a unique subset of lesions with biologically different behaviour, in that the neck nodes grows faster than the primary and has more chances of developing distant metastasis. The treatment protocol for such lesions is not clearly defined in literature and is a matter of debate. Traditionally, management of the primary precedes that of the neck or the initial management of the primary dictates the management of the neck. Historically, the clinical response to non surgical curative treatment i.e. external beam radiotherapy (EBRT) with or without chemotherapy (CT), at the primary is better than at the neck, especially in N₂, N₃ nodes, which needs to be addressed subsequently in a salvage surgery either alone or enbloc with non responsive persistent primary lesion [1]. Hence in these subset of patients, surgery to address the neck prior to the treatment of primary though, oncologically unconventional, is another option

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that sounds feasible as an effective initial treatment strategy. The neck nodes response to radiotherapy (RT) is inversely related to its size [2], such that the practicing oncologist is often faced with the problem of unresolved neck metastases with an apparently clinically resolved primary. Last but not the least is the oft cited disadvantage of the troublesome morbidity associated with delayed wound healing associated with salvage neck dissection for residual disease of a N3 disease which often receives high doses of RT, in the realms of 70 Gy, to the skin and subcutaneous tissues [3]. This often leads to a prolonged hospital stay with increased costs due to higher chances of complications post-operatively. Hence considering all these limitations associated with “RT first approach” it appears feasible to offer the patient the “Neck dissection first approach” with the following advantages of, prompt wound healing and short hospital stay, prompt institution of RT to the operated neck and the primary, deemed radio-curable. Additionally in cases with adverse features such as extracapsular spread (ECS), we keep open the possibility of instituting CT together with post operative RT based on the histopathological findings of the neck dissection specimen for successful organ preservation and thus minimizing distant metastasis associated with advanced neck disease, following initial surgery (largely complication free). In this study we present our two decade experience of this treatment modality at a tertiary cancer care centre.

Methodology

A retrospective analysis of all patients who were treated with “Neck dissection first approach” followed by definitive RT with or without CT, for small primary with large neck nodes between the period of Jan 1991 to Oct 2008. A total of 109 patients were identified to be included in the study, who were biopsy proven T₁, T₂ SCC of the UADT (hypopharynx, oropharynx and supraglottis), treatment naïve, deemed radiocurable after detailed clinically, endoscopic and radiologic (with cross sectional imaging) evaluation, with large N₂, N₃ neck node. After excluding small primary with unfavourable portents, such as deeply infiltrative morphology and large necrotic component, bilateral neck nodes (N_{2c}) and unresectable neck disease or those considered unfit for chemoradiation. Appropriate informed consent was taken after counseling the patient about all aspects of the total management, i.e.; upfront neck dissection followed by post-operative EBRT to bilateral neck with/without CT. Evaluation included a complete clinical examination, routine blood investigations and chest X-ray, apart from other investigations to rule out distant metastasis. The patients were subjected to direct laryngoscopic evaluation under general anesthesia for accurate evaluation

of the tumor morphology and biopsy from the primary for histological confirmation. Comprehensive neck dissection (Levels 1–5 clearance) was performed on these patients on priority basis after which RT with or without CT was initiated. RT for primary was given at 64–70 Gy in 32–35 fractions and that to the neck at 60–66 Gy in 30–33 fractions with spinal cord sparing after 45 Gy. A boost of 5 Gy was directed to the primary site as well as the operated neck bed in event of ECS and/or possibility of microscopic deposits secondary to R₁ resection. The RT was administered after immobilization of the patients for 5 days a week with weekly cisplatin at 40 mg/m² by intravenous bolus in patients with N₃, based on the study by Bernier et al. and Cooper et al. [2, 4]. The median follow up period was for 24 months (range: 10–72 months). The results were analysed using the SPSS statistical software package.

Results

Of the total 109 patients 93 were males and 16 were females, with a median age of 54 years (range:32–70 years).The most common presentation was neck swelling ($n = 94$) followed by odynophagia ($n = 28$) with a mean nodal size of 4.5 cms. The primary was commonly seen in oropharynx followed by hypopharynx and supraglottis (Fig. 1) and all had nodal presentation, with predominantly N₂ disease (Fig. 2). Neck dissection was done on priority by about the 10th day from the date of first visiting the OPD (range:5–30 days), in the form of comprehensive neck dissection (MRND = 39, RND = 55). Complete nodal clearance was achieved in 94 patients. There were no significant post-operative complications except for chyle leak in seven patients and seroma in four patients, which were managed conservatively without increasing hospital stay. Histopathology report of the neck dissection specimen was squamous cell carcinoma (SCC), of which 32 were poorly differentiated, 48 moderately differentiated and 14 well

Fig 1 Location of UADT primary sites

Fig 2 TNM stage of the disease

differentiated. ECS was seen in 85% ($n = 80$) of the patients. External beam RT was initiated following surgery usually on an average by the 26th day (range: 20–60th day) after complete wound healing. Of the total 109 patients only 94 were included in the study and the remaining 15 were excluded from the study as eight patients did not complete treatment due to RT and/or CT related complication, four patients defaulted on treatment and the remaining three patients died due to other causes. There were treatment breaks in 14 patients, especially in those receiving chemoradiation, in the form of grade 2 and 3 mucositis (38%), but all these patients completed their treatment (after appropriate Gap correction) and received symptomatic treatment for their conditions. Of the 94 patients in the study 24 patients received concomitant CT + RT. Local control was achieved in 79 patients (84%), regional control in 61 patients (65%). 18 patients developed distant metastasis, of which five patients had received chemoradiation and the remaining only RT. The common site being lung (11), followed by liver (5) and bone (2). It was noted that the regional recurrence and distant metastasis was common in patients with N3 neck nodes. At median follow up of 24 months, disease free survival (DFS) was seen in 70% of the patients and overall survival (OS) in 61% (5 years).

Discussion

SCC of the UADT especially oropharynx, hypopharynx and supraglottis owing to rich lymphatic network have a high predilection of neck nodes metastasis even when the tumor volume of the primary is small. Neck nodes are the single most important prognostic factor in HNSCC affecting survival and ECS is directly proportional to the size of the node and this in turn is directly proportional to the incidence of distant metastasis and thus survival [5, 6]. Radiocurability of the neck nodes decreases with increasing nodal size (N_1 – N_3 :100–23%) [1]. RT alone does not control large volume neck disease and regional failure

ranges from 30% in N2a nodes to 70% in N3 nodes [7]. Delay in salvage treatment to control the neck owing to delayed presentation to the clinic as well as rapid tumor growth leading to non resectable neck nodes will adversely impact survival; thus the concept of “*Neck dissection first approach*” followed by definitive RT with or without CT seemed singularly attractive [8, 9]. There is little doubt that surgery needs to be incorporated in treatment plan of patients with N_2 – N_3 neck nodes, though the timing of neck dissection has traditionally been after completion of definitive EBRT and after ascertaining the cure of the apparently radiocurable primary lesion. The conventional treatment modalities include, surgery for both primary and neck followed by post operative RT or radical RT with or without concomitant CT for both primary and neck followed by planned neck dissection for residual neck disease [10]. The option of “*Neck dissection first approach*” followed by RT to both primary and the neck though unconventional is a practical option because of the gratifying loco-regional control even with high incidence of ECS. The treating oncologist should consider this treatment option too for patients with small primary with large neck nodes, though some believe that surgery changes the lymphatic drainage leading to high risk of aberrant or retrograde lymph node metastasis. There is no definitive evidence in literature to justify the superiority of one particular approach over the other. The advantage of “*Neck dissection first approach*” followed by definitive RT are as follows: surgery is technically simple to perform in a non-irradiated neck with lesser incidence of any of the post operative complications; the caveat being RT has to be initiated early without overt delay (prior to onset of fibrosis) which would affect the treatment outcome. However, appropriate primary tumor selection with respect to “radiocurability” is crucial as is good patient compliance to the treatment plan. Delay in starting RT was shown to affect survival in a study by Byer’s et al. and Vikram et al. [11, 12], whereas it did not seem to have an effect in another study by Smeele et al. [13]. Average time for commencement of RT following the surgery for neck in our study was 26 days. The advantage of administering RT followed by surgery is that the primary is addressed at the same time; on the contrary this does away with the drawback of performing surgery in an irradiated neck which may be technically difficult due to the associated hyperemia and fibrosis. Even in patients who have complete response at the primary with decrease in size of the neck node clinically this may lead to a sense of complacency both amongst the treating oncologist and the patient, who may depend on a wait and watch policy. It is important to ‘delink’ the management of the primary from that of the neck once control at the primary is assured by clinical examination and endoscopy as it is well documented that

CR at end of RT in lesions staged T1-2 is maintained in 80% of the cases and culminates in long term primary control [1]. It stands to reason that concomitant CT additionally consolidates local control with recent reports of diminished distant spread especially in those deemed high risk Viz with ECS [14]. It is well documented that in such situation dissecting the neck with apparent clinical complete response may yield microscopic residual disease in 25–30% of the resected specimen [15].

In our analysis of the management of patients with small primary and large neck nodes, we found that most common site of the primary was the oropharynx followed by hypopharynx (Fig. 1). The neck nodes were predominantly N₂ ($n = 80$) (N_{2a} = 54, N_{2b} = 26) and the primary was T₂ ($n = 65$). Patients were subjected to “*Neck dissection first approach*” after compliance with inclusion and exclusion criteria. On priority basis neck dissection was done, with minimal post operative complication, and were subsequently subjected to definitive RT for primary and neck without delay as advised by Byers and Vikram [11, 12]. During the course of RT there were treatment breaks in 14 patients, who were managed conservatively and could complete their scheduled treatment. The treatment breaks were noted more so in patients receiving concomitant chemoradiation. Chemoradiation apparently showed lower incidence of distant metastasis with no significant impact on survival in our analysis of data.

In the present study there was 84% local control, 65% regional control, 19% distant metastasis. DFS (after minimum of 24 months follow up) was at 70% and OS (5 years) of 61%. The failure was often seen in the neck rather than in the primary, especially in T₂ N₂ lesions. Considering that 85% of the nodes showed ECS this regional failure is understandable. More important is to make an important judgement call with respect to radiocurability of the primary purely on the clinical, endoscopic and radiologic grounds. Needless to state this requires a lot of clinical acumen which can be acquired by long experience with the biology of these neoplasms. Our results are comparable with those achieved in other studies found in the literature, such as the one by D’cruz et al. [16], which was a prospective study of 59 patients with a radiocurable pharyngolaryngeal primary with large neck nodes, and a median follow up of 25 months, were the DFS and OS was 54 and 60%, respectively. Byers et al. [11] retrospectively reviewed 35 patients for a similar subset of patients, their regional failure rate was 11% and a 5-year survival was 55%. They also showed that delay in starting RT after the initial surgery for the neck was associated with decreased survival. One of the initial studies of treating the small primary with advanced neck disease by the French Head and Neck study group [8] of 65 patients showed 9% local recurrence and 4% regional recurrence with a median

follow up of 19 months and Verschuur et al. [9] had a 20% local recurrence in a retrospective study of 15 patients whereas Allal et al. [17] showed in a retrospective study of 24 patients a 3 year actuarial locoregional control of 73%. Reddy et al. [18] in a retrospective study comprising 16 patients had a DFS of 93.75% and OS of 100% with a follow up ranging between 6 and 78 months.

Conclusion

Though the concept of split therapy or “*Neck dissection first approach*” is not new, this article is an attempt to come out with nearly two decades of experience at a tertiary cancer referral centre with a subset of patients in whom decision making could be tricky. We conclude that in the present era with the availability of better CT agents and better techniques to deliver RT, the “*Neck dissection first approach*” would still be appropriate in N2 (especially N2b) and N3 necks with small primaries followed by RT/CT + RT, in those patients where R0 resection is possible and are compliant to the adjuvant treatment protocol including the follow up and without much delay in initiating the adjuvant treatment. A high number of primary site conservation can be achieved with reasonable regional control with this protocol. The role of treatment intensification with concomitant and maintenance CT should be explored in view of the high incidence of distant metastasis with locoregional controlled disease. A randomized controlled trial comparing the treatment options for these group of patients with small primary and big neck node, would be ideal to solve the questions surrounding the “*Neck dissection first approach*”.

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