European Archives of Oto-Rhino-Laryngology (2019) 276:567–574
https://doi.org/10.1007/s00405-018-5253-4

HEAD & NECK

Outcome of patients following neo-adjuvant chemotherapy for unresectable cervical nodes in head and neck squamous cell carcinomas

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Received: 6 September 2018 / Accepted: 12 December 2018 / Published online: 17 December 2018

Abstract

Background This study was undertaken to assess the effects of neo-adjuvant chemotherapy (NACT) on patients with head and neck squamous cell carcinoma (HNSCC) having advanced unresectable cervical nodal metastasis.

Methodology A retrospective cohort study was conducted to assess the response of unresectable nodes to NACT in a pragmatic manner. Patients were grouped according to the response noted and the treatment offered after chemotherapy. The median survival amongst the patients in these groups was compared.

Results The study included 51 patients. Oral cavity was the commonest site (67.2%). Favourable nodal response was seen in 64.7% of the patients. Up to 87.9% of the nodal responders were amenable to curative intent therapy. The overall survival of patients undergoing surgery, definitive chemoradiotherapy, palliative chemotherapy and palliative radiotherapy was 24, 13, 10 and 9 months, respectively.

Conclusion NACT may be utilized in HNSCC with advanced inoperable nodal disease to make them amenable to definitive therapy.

Keywords Induction chemotherapy · Head and neck cancers · Unresectable nodes · Response

Introduction

Locally advanced head and neck squamous cell carcinoma (HNSCC) requires multi-modality treatment [1]. Such a treatment may include a combination of surgery, radiotherapy or chemotherapy. These cancers may not always be amenable to upfront definitive therapy [2]. Neo-adjuvant chemotherapy (NACT) has often been utilized in such a setting with variable results. It has been shown to have survival advantage in hypopharyngeal cancers and advanced head and neck cancers [3–5]. It is also been used for borderline resectable oral cancer primary tumors to render them amenable for surgical excision [6]. Occasionally, it is not the primary lesion but the nodal disease which may be advanced and inoperable. There is sparse literature on the impact of NACT on nodal disease. Thus, we undertook this study to assess the effect of NACT on patients with HNSCC having advanced unresectable cervical nodal metastasis.

Methodology

This was a retrospective cohort study where analysis of a prospectively maintained database at a tertiary cancer care centre was done. It included all the patients with HNSCC who received NACT for their nodal disease between January 2012 and December 2015. The patients having unresectable primary disease were excluded. We excluded all the patients who received NACT for any indication other than their extensive nodal disease, as well as those who had

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recurrences or second primaries or non-squamous histology or nasopharyngeal carcinoma. Patients whose pre-NACT and post-NACT disease status was not documented or had incomplete clinical records were also excluded from the study. All patients with oropharyngeal carcinoma had their HPV status assessed by immunohistochemistry for p16.

The treatment decisions for all the patients were taken in a multi-disciplinary joint clinic where the surgical oncologist, medical oncologist and radiation oncologist were present. The reasons for NACT for nodal disease were (a) fixed cervical nodes, which had gross extracapsular spread with fixity to underlying structures having extensive skin, soft tissue involvement along with involvement of the underlying muscles (deep muscles of the neck, pre-vertebral fascia)/cartilage (hyoid, larynx)/bone (mastoid, clavicle); (b) large nodal disease encasing carotid artery > 180° rendering them unresectable. Only patients with unresectable cervical nodes, irrespective of their nodal stage or primary disease, were considered for analysis. Distant metastases were ruled out in all cases by a CT thorax or a PET scan. All clinical details were noted from the electronic medical records. The type of chemotherapy used and its details were also recorded. All the patients had a pre-NACT and post-NACT imaging in the form of a contrast-enhanced CT scan or MRI scan. The patients were said to have a nodal response to chemotherapy if there was a decrease in the largest diameter of the relevant node by at least 15%, a decrease in the angle of encasement/abutment of the carotid artery, or atleast a clinically apparent reduction in the soft tissue involvement/fixity of the node or return of mobility of the node. This clinical criterion was included because it had been observed that radiological response alone was insufficient to guide therapeutic decisions [7]. By including the subjective as well as objective criteria, we wanted to make the assessment more pragmatic and clinically meaningful. The patients were divided into two groups (nodal responders and non-responders) depending upon whether they had response in the nodes to chemotherapy. They were further classified based on the treatment offered after chemotherapy—that is, definitive concurrent chemoradiation (CTRT), surgery, palliative chemotherapy or palliative radiotherapy. All the patients were reviewed by a multi-disciplinary team after NACT. Amongst those who showed response, surgery followed by adjuvant was considered for those sites whose primary modality of treatment would have been surgery. These included patients having oral cavity cancer. Definitive CTRT was considered for those sites for whom primary treatment would have been chemoradiation. These included patients having malignancy of the oropharynx, larynx or hypopharynx. Those oral cavity cancer patients, who had showed a response to NACT and had good performance status but were still unresectable, were considered for chemoradiation. Patients having CUPS who showed a very good response to chemotherapy were considered for chemoradiation, whereas others showing a partial response were considered for surgery.

In patients who underwent surgery after NACT, pathological response was assessed at the time of histopathological assessment. Adjuvant chemoradiation was advised for all the patients who underwent surgery following NACT.

Chemotherapy combinations utilized for NACT included either docetaxel with cisplatin or docetaxel, cisplatin and 5-fluorouracil or paclitaxel and carboplatin. The regimen for CTRT consisted of 70 Gy radiotherapy given in 35 fractions along with 3-weekly cisplatin. The palliative radiotherapy was given as either 40 Gy in 16 fractions or 30 Gy in 10 fractions. Post-surgery adjuvant chemoradiation regimen consisted of 60 Gy radiotherapy in 30 fractions along with 3-weekly cisplatin. Drugs used for palliative chemotherapy included paclitaxel with carboplatin delivered weekly in the majority of the cases and oral metronomic chemotherapy (oral methotrexate 15 mg/m^2 once a week and oral celecoxib 200 mg twice daily) in two patients. The median survival between these groups was compared. The AJCC 7th edition TNM staging was followed. The follow-up details of all the patients were recorded till December 2017. If details were not available on the electronic medical records, then the patients were contacted telephonically and requested to follow up in the outpatient department where their disease status was evaluated. The status of the patients at the time of the last follow-up was considered as the final status. The status of the disease was noted as locoregionally controlled or as having residual/recurrence/metastases. In patients diagnosed to have recurrence, the date of performing the investigation to confirm the recurrence was considered as the date of recurrence. The pattern of recurrence was noted. Overall survival was calculated from the date of registration to the date of last follow-up or the date of death of the patient. All statistical analyses were performed using SPSS version 21. Survival analysis was done using Kaplan–Meir analysis. As the study involved only retrospective analysis of the prospectively collected data with no intervention in the patients, institutional review board and ethics committee approval was taken and consent waiver was obtained. The study was in compliance with the Helsinki Declaration.

Results

136 patients received NACT for their nodal disease between January 2012 and December 2015. Out of these, 51 patients fitted our inclusion criteria and were considered for analysis. Their age group ranged from 24 to 77 years with a median age of 49 years and the majority of them were males (82.4%). 96% of them received NACT for fixed unresectable nodes, and 4% had the nodal mass encasing the carotid at > 180°. The majority (58.8%) received two cycles (3 weekly)

of a two-drug regimen of cisplatin with docetaxel, 23.5% received two cycles of cisplatin (3 weekly) and docetaxel 5FU, and 13.7% received six (weekly) cycles of paclitaxel with carboplatin. The most common site of disease was the oral cavity (67.2%) followed by CUPS and oropharynx (13.7% each), larynx in 5.9% and hypopharynx and PNS primaries in 2% each (Table 1). All the oropharyngeal cancer patients had HPV-negative tumors.

On evaluating the nodal response to NACT, 64.7% had significant nodal response, whereas 35.3% patients were non-responders. Amongst the non-responders, 13.7% had stable disease and the remaining 21.6% had nodal progression. Amongst the nodal responders, 60.8% had partial response and 3.9% had complete nodal response. Post-NACT, even amongst the responders, 12.1% patients were not found to be suitable for definitive therapy. This was because out of these four patients, three had a differential response at the primary site. In spite of the partial response noted in the lymph nodes, their primary lesions progressed and became unresectable. Hence, they were treated with palliative intent. The fourth patient had poor performance status, making him unfit for definitive therapy. The remaining 87.9% patients received curative intent primary therapy in the form of either surgery (33.3%) or concurrent chemoradiation (54.5%). Two patients defaulted treatment on their own. Of the entire cohort, 39.2% were not found suitable to complete definitive therapy and hence received palliative intent therapy, with palliative chemotherapy in 55% (11/20) and palliative radiotherapy in 45% (9/20) of the patients (Fig. 1).

Table 1 Demographic details

Factors	Percentage (number of patients) ($n=51$)
Sex	
Male	82.4 (42)
Female	17.6 (9)
Age	
Median	49 years (range 24–77 years)
Subsite	
Oral cavity	62.7 (32)
CUPS	13.7 (7)
Oropharynx	13.7 (7)
Larynx	5.9 (3)
Hypopharynx	2(1)
PNS	2 (1)
Clinico-radiographic T stage	
T0–T2	33.3 (16)
T3–T4	66.6 (35)
Clinico-radiographic N stage	
N2a	11.5 (6)
N2b	11.5 (6)
N2c	15.4 (8)
N3	61.5 (32)
Reason for NACT	
Hard, fixed nodes	96 (43)
Extensive encasement of the carotid artery > 180	4 (2)

In those (11 patients) who underwent surgery, 10 had a primary in the oral cavity and 1 had CUPS. In patients who received CTRT, seven patients had a primary in the oropharynx, five in the oral cavity, three had CUPS, two had laryngeal and one had a hypopharyngeal primary. Post-surgery histopathological analysis showed that none of the patients had a pathological complete response in the lymph nodes. All of them had only a partial response to the NACT. The response at the primary site was not evaluated for this analysis, as none of the patients had any operability issue with respect to the primary lesion and the aim of our study was to assess the response in the nodes (Fig. 1).

Amongst those treated with curative intent (29 patients), one patient could not complete definitive chemoradiotherapy due to poor performance status. Local, regional and locoregional failures were seen in 6%, 42.4% and 12.1% patients, respectively. Distant metastasis developed in 13.7% of the patients. 9% patients in the surgical group developed distant metastasis. In the definitive chemoradiation group, 16.7% patients developed distant metastasis. Mean time to distant metastasis was 5.3 months and 8.5 months in the surgery and the chemoradiation groups, respectively. Amongst those treated with palliative intent, 25% of the patients developed distant metastases (Fig. 1).

The median overall survival (OS) of the entire cohort was 10 months (7.1–12.8; 95% CI). It was highest in the group who underwent surgery, with a median OS of 24 months (7.8–40.1; 95% CI), followed by those who received CTRT—13 months (6.8–19.1; 95% CI). OS of those who received palliative chemotherapy was 10 months (5.9–14.0; 95% CI) and OS of those who received palliative radiotherapy was 9 months (5.2–12.7; 95% CI) (Fig. 1). The Kaplan-Meier curves showing the overall survival curves are shown in Fig. 2.

Discussion

Neoadjuvant chemotherapy has been used for a wide variety of indications in head and neck cancers. Its use, though controversial at times, has continuously been evolving. The Veterans Affairs trial demonstrated that NACT can help in laryngeal preservation [8]. The long-term results of RTOG 91-11 trial on subjects with laryngeal cancer proved that

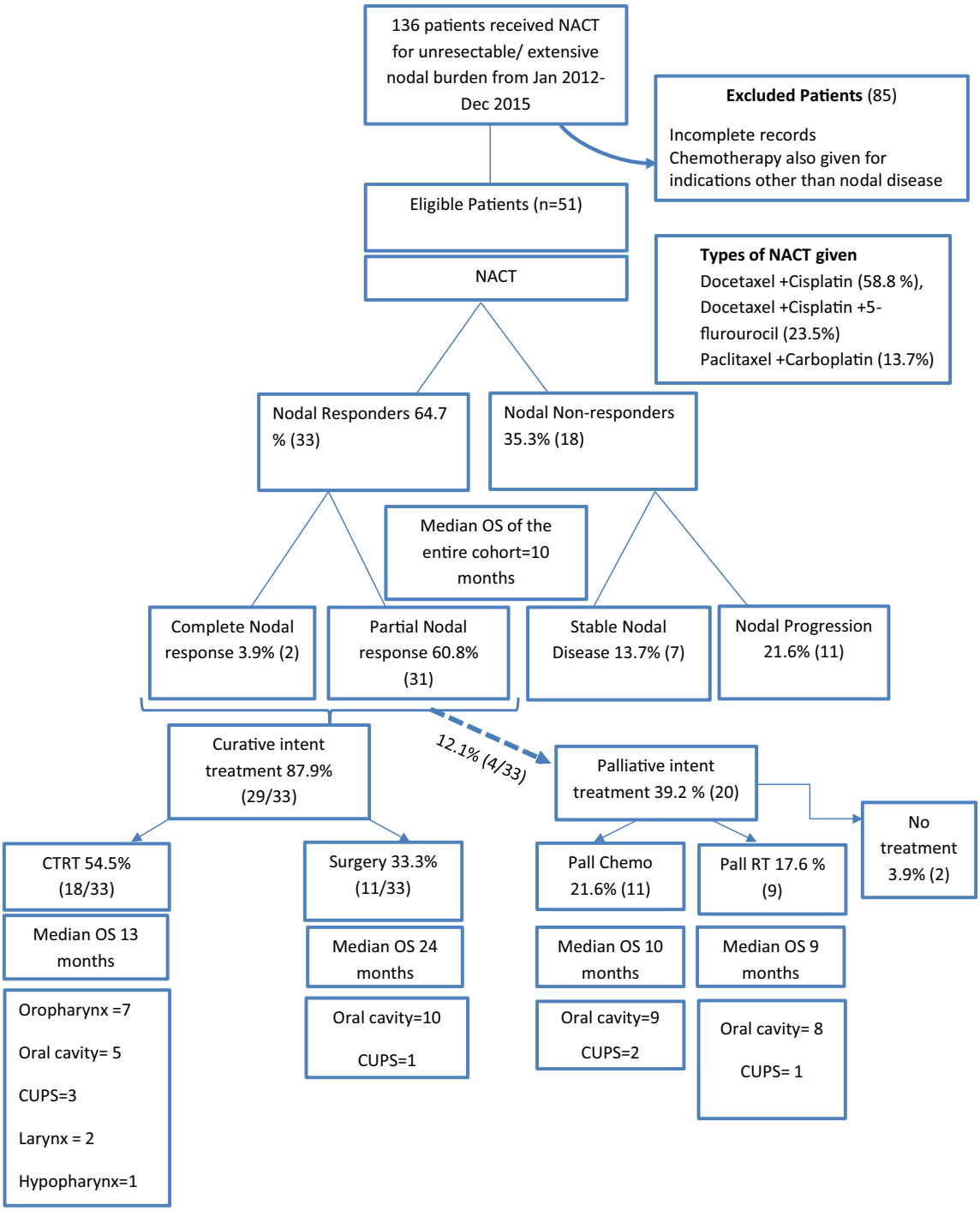

Fig. 1 Flowchart showing the study methodology, response to NACT, intent and type of final therapy received with survival and sub-site distribution (*NACT* neo-adjuvant chemotherapy, *OS* overall survival, *CTRT* concurrent chemoradiation, *CUPS* carcinoma of unknown primary site)

concurrent chemoradiation was more beneficial than NACT with respect to locoregional control and laryngeal preservation [9]. NACT has been tried in operable oral cancers, but has not shown any survival advantage [10, 11]. It was observed that NACT in such cases can help in preserving mandible and also reduce the need of receiving adjuvant therapy [10]. NACT using three drugs (as compared to two) has shown to improve survival in inoperable and other locally advanced HNSCC [5, 12]. A recent meta-analysis has shown that there is no advantage in OS, disease-free survival or recurrence when NACT was used for resectable HNSCC [13]. Another recent phase II–III randomized controlled trial

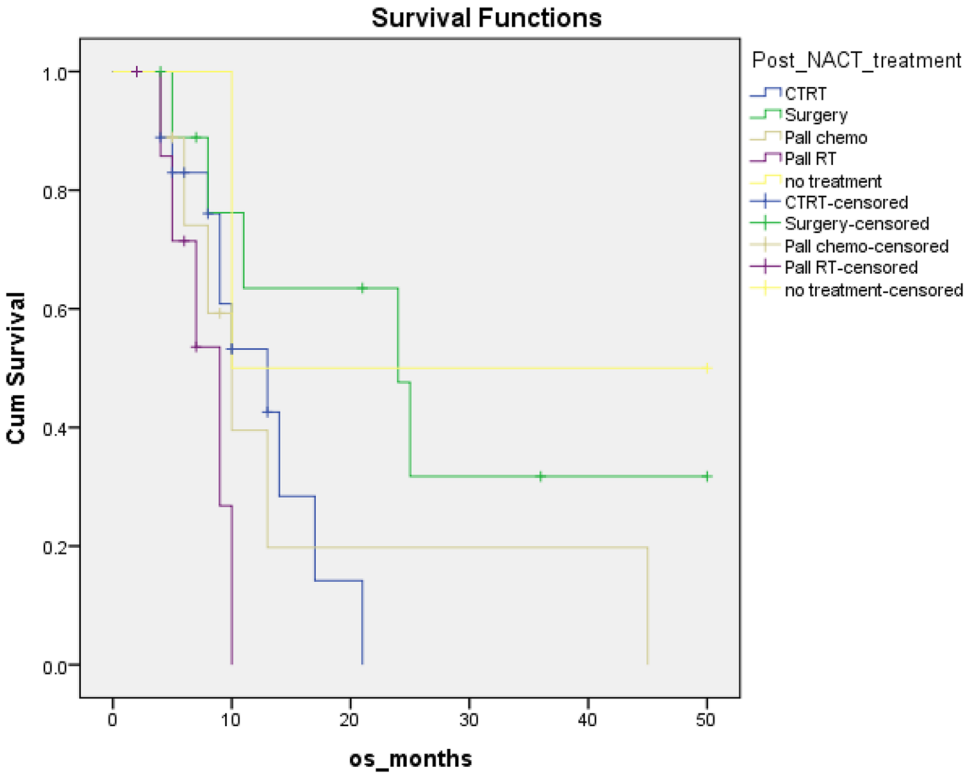

Fig. 2 Kaplan–Meier curve showing the overall survival in patients who received NACT for their nodal disease compared on the basis of final therapy received

has shown survival advantage in locally advanced head and neck cancers [14]. Currently, NACT is more often utilized in borderline operable oral cancers [6, 15]. One study with a large sample size of 721 patients demonstrated that 66.2% patients became resectable after using a three-drug NACT regime.

There are very few studies which have specifically looked at the nodal response to chemotherapy. The TAX 324 study in their sub-group analysis of N3 patients found that those treated with TPF had better median overall survival (OS) than those treated with PF alone (37 months versus 12 months), though no statistically significant difference was seen [5]. In a subgroup analysis of another randomized trial comparing NACT with upfront surgery in resectable oral cancers, the group with cN2 nodal stage showed improved OS and disease-free survival [16]. Another retrospective study has looked at NACT for N3 nodes. They found that patients who received NACT had better OS than those who received either definitive CTRT or surgery (50% vs 16%, $p < 0.001$). The majority of patients in this study had oropharyngeal primary with unknown HPV status. There was no clear mention of how the response was assessed. Whether the nodes were upfront operable or amenable to definitive therapy was also not mentioned. Furthermore, the cases ranged over three decades and there have been major paradigm changes in the treatment protocols, radiotherapy, chemotherapy and surgery over these years [17]. The only study which attempted to provide level I evidence on the role of NACT for nodal disease was a phase III randomized controlled trial (DeCIDE), which evaluated the role of NACT in N2 and N3 HNSCC with the primary end point as OS. However, the actual response to the nodal metastasis was neither their primary nor the secondary end point. Moreover, in 17.3% patients, the pre-NACT data were not available. They found that there was nodal response to NACT in 64% patients. The majority of patients in the induction chemotherapy arm in this study had oropharyngeal primaries (61.3%) and only 15% had oral cancer (whose primary modality of treatment was surgery). Both the arms of this trial were planned to receive concurrent chemoradiotherapy as the definitive management. Thus, this study was unequipped to assess the advantages gained by surgery after induction chemotherapy in these patients. The study included only 11% N3 cases; the rest of the patients had N2 nodal disease. They also did not mention whether these nodes were resectable at the time of presentation and hence fail to represent the clinical scenario of an HNSCC with inoperable or advanced nodal disease and the role of NACT in such cases [18].

It has been long known that with increasing nodal size or volume, the chance of achieving regional control with radiotherapy decreases [19]. The response of lymph nodes > 6 cm to primary radiotherapy alone has been found to be about 45% at 2 months [20]. It has been shown that for N3 nodes, adding neck dissection to chemoradiation decreases the chances of regional failure and improves

survival [21]. Utilizing definitive chemoradiation in such settings requires much larger doses and is associated with higher risk of complications [22, 23]. We would also like to stress on the point that the size or the volume of the node is not the only criterion which would make us consider NACT. The nodal disease may be fixed to underlying structures such as the carotid vessels, hyoid, nerves and/or extensively involve the overlying skin and soft tissues. We included all these patients in our analysis. The radiological response to NACT is mostly assessed via response evaluation criteria in solid tumors (RECIST). To assess the nodal response, the RECIST 1.1 measures the sum of the short axis of all the nodal target lesions [24]. It has been observed that the response noted in the RECIST criteria may not actually help in the clinical decisions. The decision regarding further therapy is often based upon the actual clinical response, besides the planes with carotid, hyoid, pre-vertebral fascia on the radiology reinforce this [7]. A study on borderline operable oral cancers observed that even though RECIST showed stable disease, 30% of these patients still underwent surgical resections [6]. Another study has shown that there is great discordance between radiological response rates and surgical decision making, and there was no linear correlation between radiological size decrement and tumor response [7]. In our study, we used a 15% change in the greatest diameter of the node, degree of abutment with carotid and a clinically apparent reduction in soft tissue involvement or mobility of the node to assess the response. We believe that these criteria are more important while assessing the response of nodes to chemotherapy. Thus, a combination of radiological and clinical response was utilized for decision making to make the assessment more clinically meaningful.

We observed that in 64.7% patients nodes had a response to chemotherapy. This was quite similar to the response seen in a phase III trial assessing response to NACT in N2/N3 nodes [18]. Out of the entire cohort, 56.8% (29/51) or 87.9% (29/33) amongst those showing nodal response were deemed suitable for definitive curative intent therapy after NACT. The definitive therapy was in the form of concurrent chemoradiation or surgery. 12.1% (four) patients in spite of having partial response were not found suitable for definitive therapy. Amongst the non-responders (35.3%), two-thirds patients had nodal progression. Based on the performance status, palliative therapy in the form of palliative chemotherapy was given to 21.6% (11/51) patients and palliative radiotherapy was given to 17.6% (9/51) patients.

Those who underwent surgery had the best median overall survival (24 months), followed by the definitive CTRT group with median overall survival of 13 months. In the palliative intent group, the palliative chemotherapy group had a slightly better median OS of 10 months as compared to palliative RT with a median OS of 9 months. These differences in the OS did not reach statistical significance, probably due to the small sample size. In patients undergoing surgery, the tumor and the nodal disease were removed and all these patients received adjuvant chemoradiation. This was in contrast to the patients in the group who received definitive CTRT alone. This could account for better survival seen in patients undergoing surgery.

In a study on unresectable oral cancers who received NACT, the median survival of the patients who were resected following NACT was significantly better (19.6 months) than those treated non-surgically (8.16 months) [6]. In our study too, NACT proved advantageous for about 33% patients who could undergo surgery after NACT and thus had better OS. The few studies which have looked at the role of NACT for nodal disease have mostly treated the patients with CTRT after NACT.

In our study, the majority of patients had a primary for which surgery was the treatment of choice. So our results also provide evidence of using NACT in such a group of patients who would require surgery later on. A recent review of N3 patients from the National Cancer Database showed that survival outcome was better for those who underwent surgery [25]. Few other studies have also showed similar results [26, 27]. It is emphasized that surgery is usually selected when the nodal diseases as well as the primary are amenable to resection. Amongst these, a subset of patients with unresectable nodal disease may be benefitted by NACT, as it will facilitate definitive therapy in the form of surgery. Our study showed similar results, as patients who could undergo surgery after NACT had better survival.

It has been observed that in patients with N2–N3 nodes even after complete radiologic response to definitive CTRT, the initial failure is often due to distant metastasis (upto 28%). Induction chemotherapy may prove beneficial in such a scenario by sterlizing micrometastasis [28, 29]. In our study, lesser distant metastasis was seen in patients showing nodal response to chemotherapy as compared to those who did not show any response (13.7% vs 25%).

We found that 56.8% patients who received NACT for nodal disease were deemed fit for curative intent therapy post-induction. It is worthwhile to highlight here that this has been one of the first attempts to evaluate the clinical utility of NACT for inoperable nodal metastasis in HNSCC. We have used a pragmatic approach to assess the response of the nodes to NACT, keeping in mind the clinical implication of the response, intent of therapy and type of definitive management.

Our study has the limitation of being retrospective in nature and the type of NACT administered was diverse. The majority of the patients received a two-drug regimen. The post-chemotherapy response assessment was on the basis of radiological and clinical assessment. This may be considered partly subjective. However, as mentioned earlier, we believe that this is one of the strengths of the study making

it clinically more relevant and pragmatic. Though a prospective study should be proposed to generate better evidence on this subject, our study does demonstrate the utility of NACT in unresectable nodal metastasis in HNSCC.

Conclusion

Cervical nodes in HNSCC show response to NACT. NACT may be utilized in HNSCCs with advanced inoperable nodal disease to make them amenable to definitive therapy.

Funding The study was a part of a self-conducted audit; no external source was utilized for any funding.

Compliance with ethical standards

Conflict of interest The authors and the institute do not have any conflict of interest in regard to the said study.

Ethical approval The study was approved by the Institutional Ethics Committee, the Tata Memorial Hospital and was conducted in accordance with the principles laid down by the 1964 Helsinki Declaration.

Informed consent As the study design was a retrospective audit, it was eligible for a consent waiver, which was obtained from the institutional ethics committee.

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