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Is Neck Dissection Necessary After Induction Plus Concurrent Chemoradiotherapy in Complete Responder Head and Neck Cancer Patients with Pretherapy Advanced Nodal Disease?

Maria Cristina Da Mosto, MD[1], Valentina Lupato, MD[1], Salvatore Romeo, MD[2], Giacomo Spinato, MD[3], Giancarlo Addonisio, MD[4], Vittorio Baggio, MD[5], Alessandro Gava, MD[5], and Paolo Boscolo-Rizzo, MD[1]

[1]Department of Neurosciences, ENT Clinic and Regional Center for Head and Neck Cancer, Treviso Regional Hospital, University of Padua, Treviso, Italy; [2]Department of Pathology, Treviso Regional Hospital, Treviso, Italy; [3]Head and Neck Department, ENT Clinic, Hospital of Cattinara, University of Trieste, Trieste, Italy; [4]Department of Radiology, Treviso Regional Hospital, Treviso, Italy; [5]Department of Radiation Oncology, Treviso Regional Hospital, Treviso, Italy

ABSTRACT

Background. The aim of the present study was to assess, in the setting of a single-institution prospective clinical trial, the necessity of planned neck dissection (PND) in physically and radiologically complete responders with pretherapy advanced nodal disease.

Methods. Between January 2000 and July 2007 a total of 139 patients were enrolled to receive a regimen of platinum-based multidrug induction-concurrent chemoradiotherapy (IC/CCRT). A total of 75 of the enrolled patients with advanced nodal disease were included in this retrospective study. Between 8 and 12 weeks from the end of treatment, the response to IC/CCRT was evaluated by fiber-optic endoscopy and head and neck contrast-enhanced computed tomography or magnetic resonance imaging.

Results. The complete clinical response (cCR) rate was 68 %. Among the 51 patients who achieved locoregional cCR at the end of CCRT, 8 underwent PND according to the study recommendation. Of the 43 patients with cCR who did not undergo PND, 2 patients (4.7 %) experienced isolated regional recurrences with the 5-year regional control being 82 %. Patients with cCR did not have a significantly lower regional control compared with patients with cCR who underwent ND ($P = .962$). Pathological evidence of residual disease was found in 81 % of the patients with less than cCR who underwent ND.

Conclusions. In physically and radiologically complete responders to IC/CCRT, a PND appears not justified. Conversely, PND should be performed in patients clinically suspected of having residual disease in the neck, as a significant proportion have viable tumor cell in post CCRT ND.

The treatment paradigm of locoregionally advanced head and neck squamous cell carcinoma (LA-HNSCC) has progressively evolved from radical surgery followed by radiotherapy (RT) to the current application of nonsurgical organ preservation strategies, involving administration of chemoradiotherapy (CRT). Surgery is nowadays reserved as a salvage procedure for patients with persistent or relapsing tumors.[1]

In this new scenario, the management of the neck after definitive CRT is still a matter of debate. The question revolves around the appropriateness of a planned neck dissection (PND) for clinical complete responders with pretherapy advanced nodal disease (N2–N3). In fact it is generally accepted that patients with initial N1 neck obtaining clinical complete remission (cCR) do not require PND.

Among the reasons underlying this controversy are the lack of data from randomized clinical trials, the difficulty of estimating nodal response after an organ preservation strategy, and the fact that in many institutions PND was historically the standard of care when treating patients with advanced nodal disease with conventionally fractionated RT alone because of the low rate of complete remissions and modest results of salvage surgery.[2] In fact, the contemporary improvement in local and regional control

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P. Boscolo-Rizzo, MD
e-mail: paolo.boscolorizzo@unipd.it

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achieved using concurrent administration of CRT with or without neoadjuvant chemotherapy and the refinement of posttreatment radiological imaging have prompted some authors to consider obsolete the concept of PND after cCR to chemoradiation.[2,3]

We recently reported clinical results from our nonrandomized phase II study evaluating the efficacy and safety of a regimen of platinum-based multidrug induction-concurrent CRT (IC/CCRT).[4] The aim of the present study was to assess, in the setting of this single-institution prospective clinical trial, the necessity of PND in physically and radiologically complete responders with pretherapy advanced nodal disease.

PATIENTS AND METHODS

Between January 2000 and July 2007 a total of 139 patients were enrolled to receive cis-platinum based IC/CCRT for LA-HNSCC at Treviso Regional Hospital. Following 1 cycle of IC with cis-platinum (100 mg/m^2) and 5-fluorouracil (1000 mg/m^2/day), 2 cycles of cis-platinum (100 mg/m^2) and 5-fluorouracil (1000 mg/m^2/day) concurrently with definitive RT up to a dose of 66–70 Gy were administrated, regardless of the response to induction chemotherapy. Three-dimensional conformal RT was carried out using 4- to 6-MV photons from a linear accelerator with conventional fractionation (2 Gy per fraction, once a day, 5 times a week). The dose was prescribed to the 95 % isodose according to the International Commission on Radiation Units and Measurements recommendations. The planning target volume 1 included (PTV 1) primary tumor and involved lymph nodes plus a 1.0- to 1.5-cm expansion. The PTV2 included PTV1 plus uninvolved lymph nodes at high risk of harboring microscopic metastatic disease. The prescribed dose to PTV2 was 50 Gy in N0 patients and 60 Gy in N + patients, whereas the final dose to PTV1 was 66–70 Gy. The research design and detailed methodology have been previously reported.[4]

A total of 75 of the enrolled patients had an advanced nodal disease and were therefore included in this retrospective study. Between 4 and 8 weeks after completing treatment, patients were evaluated by all members of the multidisciplinary team consisting of head-and-neck surgeons, radiation oncologists, and medical oncologists to assess the response to IC/CCRT. cCR to therapy was defined as disappearance of all measurable and evaluable disease within the treatment field as assessed at 8–12 weeks after therapy by fiber-optic endoscopy and imaging studies, that is, head and neck contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) according to RECIST criteria.[5] MRI was performed particularly in patients with SCC of the oropharynx or oral cavity.

CT scan was performed using multislice CT with a collimation of .7 mm and a reconstruction interval of 1 mm before and after intravenous administration of iodine contrast agent using a biphasic injection protocol: 90 ml at a flow rate of 2.5 ml/second and then 30 mL at 1 ml/second. MRI examinations were performed on a 1.5-Tesla scanner. The chosen section thickness was 3 mm, with an interslice gap of .4 mm using T1-weighted images before and after injection of intravenous gadolinium, T2-weighted and diffusion-weighted on axial, sagittal, and coronal plane. The main criteria for neck metastases on CT and MRI investigations performed during staging and at 8–12 weeks after treatment were: presence/persistence of heterogeneous contrast enhancement, presence/persistence of central necrosis, round node shape, short diameter of submandibular nodes, and other regional neck nodes >15 mm and 10 mm, respectively, presence/persistence of high signal on diffusion-weighted MRI with low apparent diffusion coefficient.

The study protocol recommended ND for patients with high-volume node metastasis (>3 cm) regardless of the response to therapy. However, shortly after the start of the study, the application of posttherapy ND in physical and radiological responders was abandoned according to pathological findings showing no evidence of viable tumor cells (VTCs) in the neck of all patients who underwent PND.

The routine follow-up program consisted of locoregional examination at 2-month intervals during the first year, 3-month intervals in the second year, 4-month intervals between the third and fifth year, and every 6 months thereafter.

Patients' and tumor's characteristics were summarized by descriptive measurements (median, range, and proportion). The 2-sided confidence intervals (CIs) according to Wilson method were calculated for response and disease control rates. Time-to-event data were described using Kaplan–Meier actuarial curves and compared by log-rank test. Regional control (persistent disease or regional recurrence considered as an event), overall survival (OS, death of any cause considered as an event) and progression-free survival (PFS, recurrence or progression and death considered as an event) were measured from the date of enrollment.

Statistical analyses were conducted using the SPSS/PC statistical program (version 18.0 for Mac; SPSS Inc., Chicago, IL) and the confidence interval (CI) analysis program CIA. The study was conducted under ethical guidelines.

RESULTS

Demographics

Table 1 shows demographics and tumor characteristics of the 75 patients.

TABLE 1 Patients' and tumor's characteristics ($n = 75$)

Patients characteristics	*N*	%
Age (years)		
Median	61	
Range	39–77	
Gender		
Male	65	86.7
Female	10	13.3
Site primitive tumor		
Oral cavity	5	6.7
Oropharinx	46	61.3
Hypopharynx	12	16.0
Larynx	12	16.0
Stage of primary tumor		
T2	24	32.0
T3	19	25.3
T4	32	42.7
Nodal stage		
N2a	36	48.0
N2b	20	26.7
N2c	9	12.0
N3	10	13.3
Overall stage		
IVa	53	70.7
IVb	22	29.3

Response to Treatment and Pattern of Failure

Overall, 65 patients (88 %) received ≥66 Gy and ≥80 % of the planned cisplatinum and 5-FU doses. A median total dose of 66 Gy (range, 52–70 Gy) was administered. There were 9 patients who received a dose of RT <66 Gy.

A total of 51 patients obtained a cCR both on primary and neck sites. Also, 9 patients and 5 patients achieved a cCR on primary site and neck site alone, respectively. The overall physical and radiological response rate at 8–12 weeks postchemoradiotherapy was 92 % (95 % CI 84 %–96 %), with a cCR rate of 68 % (95 % CI 57 %–77 %) and a clinical partial response (cPR) rate of 24 % (95 % CI 16 %–35 %). The overall nodal CR rate was 74 % (95 % CI 64 %–83 %). The nodal CR rate was 78 % (95 % CI 67 %–87 %) for N2 disease and 50 % (95 % CI 24 %–76 %) for N3 disease (Table 2).

Among the 51 patients who achieved locoregional cCR at the end of CRT, 8 underwent PND (modified radical type III ND) according to the study recommendation. In all these cases, the histopathological examination of the ND specimen revealed sclerosis or necrotic debris. Among the 5 patients who obtained a complete remission in the neck but not in the primary, 1 patient underwent salvage surgery on primary site after CRT and the other 4 patients were judged to be unresectable. Overall, 43 patients with complete physical and radiological locoregional response after IC/CCRT and advanced nodal stage at diagnosis were observed. All these patients received full dose of radiotherapy. During follow-up, 5 of these patients developed regional failure at mean of 34 months after CRT. Of those 5 patients, 3 had N2a and 2 had N3 stage at diagnosis. Isolated regional recurrences developed in 2 patients (4.7 %), both with N2a stage at diagnosis. In the other 3 patients regional failure was associated with local recurrence (2 patients) and local recurrence/distant metastases (1 patient).

TABLE 2 Tumor response to treatment

Best response	No. of patients	% (95 % CI)
Overall response rate	69	92 (84–96)
CR	51	68 (57–77)
PR	18	24 (16–35)
PD	6	8 (4–16)
Nodal CR in N2 patients	51	78 (67–87)
Nodal CR in N3 patients	5	50 (24–76)

CR complete remission, *PR* partial remission, *PD* progression of disease

Among the 19 patients who had a physically and/or radiologically suspected persistent neck disease after chemoradiotherapy, 8 patients were judged to be unfit for surgical treatment, 7 underwent salvage ND, and 4 underwent ND in conjunction with salvage surgery on primary site (radical ND or modified radical ND). In these patients, the histopathological examination of the ND specimen revealed lymph nodes metastases in 8 patients and soft tissue deposits of squamous cell carcinoma in 1 patient. In the other 2 patients histopathological examination was negative.

Post CRT NDs were performed at a median time of 12 weeks after completion of CRT (range, 10–15 weeks). No major postoperative complications were recorded in the 19 patients submitted to post CRT ND.

Among patients who were not submitted to primary salvage surgery, 3 patients required a permanent tracheotomy and 1 patient a permanent PEG, and 2 patients a permanent tracheostomy and PEG. Overall, preservation of a functional upper aerodigestive tract with intact voice and maintenance of normal deglutition was achieved in 43 patients (57 %).

Time-to-Event Data

There were 2 patients lost to follow-up. Follow-up time in survivors ranged from 26 to 120 months, with a median of 77 months. The 5-year regional control was 70 % (95 % CI 49 %–91 %). The PFS and OS at 5 years were 41 %

(95 % CI 23 %–60 %) and 48 % (95 % CI 29 %–68 %), respectively.

In the 43 patients with complete physical and radiological locoregional response after IC/CCRT and advanced nodal stage at diagnosis who were observed, the 5-year regional control, PFS and OS were 82 % (95 % CI 61 %–100 %), 59 % (95 % CI 36 %–83 %), and 64 % (95 % CI 45 %–84 %), respectively.

When comparing regional control (log-rank test, $P = .962$), PFS (log-rank test, $P = .952$), and OS (log-rank test, $P = .800$) no statistically significant differences were observed between patients with cCR who were observed and patients with cCR who underwent PND.

DISCUSSION

In the present series the rate of neck recurrences after sequential IC/CCRT in undissected patients with pretherapy advanced neck disease (≥N2), who achieved a cCR, was 11.6 %, with the rate of isolated regional failure being 4.7 %. In our opinion, this rate does not justify a systematic PND in these patients.

A number of studies have addressed the question of efficacy of PND following cCR to chemoradiotherapy in patients with high-volume neck disease. As postchemoradiotherapy ND adds significant morbidity to treatment, it should be performed in selected patients.[6] Proponents of PND note that patients undergoing nonsurgical conservative treatment have a high rate: 39 %, 28 %, 33 %, 39 %, 21 % of lymph node residual disease in neck specimens and an improved outcome with PND.[7–11] However, as noted by Ferlito et al. in a recent extensive and exhaustive review, in many of these series the evaluation of the response to treatment prior to PND was not performed or was limited to a physical assessment.[3,7–10] Therefore, many of these patients might have been probably classified as partial CR if a combined physical and radiological posttreatment evaluation were performed. A number of studies supporting a systematic PND report excellent results in terms of regional control, but none of them has clearly demonstrated that such results cannot be obtained by performing a "wait and watch" policy in appropriately selected patients.

In our series, the 5-year regional control in patients with cCR not submitted to PND was 82 %. Moreover, patients with cCR who were observed did not have a significantly lower regional control compared with patients with cCR who underwent ND ($P = .962$).

On the basis of low recurrence rates (0 %–14 %) and pattern of regional failure, several authors advocate a policy of "wait and see" in physical and radiological complete responders who presented with high-volume neck disease.[12–21] Corry et al., in a retrospective series of 60 patients with advanced neck disease who had cCR at neck site confirmed by CT scan at 12 weeks post completion of CCRT, reported no isolated neck failure despite the fact that PND was not allowed.[13] According to our results, Soltys et al. in a retrospective study of 48 patients with N2–N3 disease who achieved a physical and radiological (CT or MRI) cCR after platinum-based multidrug IC/CCRT, concluded that PND may have benefited only 4 %.[21] Furthermore, a number of studies reported no benefit on regional control and overall survival with the addition of PND in patients with cCR.[17,19,20] Recently, in a large cohort of N-positive HNSCC treated by (chemo)-radiotherapy without PND, Thariat et al. reported 92 % 5-year regional control in 377 patients who achieved a cCR.[16]

When considering pooled recent data from series using contemporary concurrent chemotherapy regimens with or without induction chemotherapy in patients with pretherapy high-volume node who obtained a radiological-based cCR and were not submitted to neck dissection (Table 3), the crude rate of regional failure is 8.0 % (95 % CI 5.7 %–11.2 %) with isolated regional failure rate being 1.6 % (95 % CI .7 %–3.4 %).

We performed the assessment of residual neck disease after IC/CCRT with contrast-enhanced CT or MRI at 8–12 weeks posttreatment. Hence, the cohort of patients who, according to study recommendations was submitted to neck surgery despite a cCR, underwent PND not earlier than 10 weeks after completion of CCRT.

The lack of consistent timing of imaging assessment and PND after organ preservation strategies as well as limitations of defining viable tumor in neck specimen may have a crucial impact in the significant variability of the reported data concerning clinical and pathological CR to CRT. The optimal timing for post CRT ND is matter of controversy. That histologic remission is an ongoing process continuing after the completion of treatment was clearly proved by Kwong et al. who, by performing serial postradiotherapy biopsies in patients with nasopharyngeal carcinoma, demonstrated that a high proportion of tumor cells detected soon after RT would disappear on subsequent repeat biopsies.[22] This may explain the discrepancy between the relatively high rate of neck positive specimen in complete responders submitted to PND and the low incidence of neck failure founded in the present and other series of patients who were observed. Stenson et al., based on the fact that the acute CRT toxicity resolves within 4 weeks of completing therapy and the onset of the chronic CRT toxicity is observed 12 weeks after CRT, have identified a "safe window" of 4–12 weeks after completing treatment for post CRT surgery.[23] On the other hand, and according to our results, the recent research by Goguen et al., comparing 67 NDs performed less than 12 weeks and 38 NDs performed 12 weeks or more after CRT, indicates that ND

TABLE 3 Pooled data of studies evaluating the rate of regional failures in patients with advanced nodal stage (*N* >N1) achieving cCR after CCRT, when no PND was performed

Authors	No. patients[a]	No. N3 patients	CRT regimen	Response assessment	Median follow-up (years)[b]	No. RF	No. IRF	No. RF in N3 patients
McHam et al.[9]	33	NS	Platinum-based CCRT	Physical plus CT	NS	4	NS	NS
Argiris et al.[17]	30	9	Paclitaxel/platinum-based CCRT	Physical plus CT or MRI	4.6	2	1	1
Brizel et al.[27]	16	NS	Platinum-based CCRT	Physical plus CT	4.0	3	2	NS
Forest et al.[18]	69[c]	11	Platinum-based CCRT	Physical plus CT	3.0	5	NS	1
Goguen et al.[19]	13	0	Platinum-based IC/CCRT	Physical plus CT ± MRI	3.2	0	0	NA
Lopez et al.[14]	12	2	Platinum-based IC/CCRT	Physical plus CT or MRI	2.3	0	0	0
Corry et al.[13]	53	8	Platinum-based CCRT	Physical plus CT	4.3	4	0	NS
Lau et al.[15]	46	3	Platinum-based CCRT	CT	2.9	3	NS	0
Moukarbel et al.[33]	12	12	Platinum-based CCRT	Physical plus CT	1.9	0	0	0
Soltys et al.[21]	48	10	Platinum-based IC/CCRT	Physical plus CT or MRI	5.4	4	1	0
Present series	43	5	Platinum-based IC/CCRT	Physical plus CT or MRI	6.4	5	2	2
Total	375	60/326 (18.4 %)				30 (8.0 %) [95 % CI 5.7 %–11.2 %]	6 (1.6 %) [95 % CI .7 %–3.4 %]	4 (7.4 %) [95 % CI 3.0 %–17.6 %]

[a] Number of patients with high-volume nodal disease who obtained clinical complete remission after CCRT and did not undergo planned neck dissection for each case series

[b] Median follow-up time of the entire case series

[c] Patients with *N* >3 cm

cCR clinically complete responders, *PND* planned neck dissection, *RF* regional failure, *IRF* isolated regional failure, *CCRT* concurrent chemoradiotherapy, *IC* induction chemotherapy, *CT* computed tomography, *MRI* magnetic resonance imaging, *NS* not specified, *NA* not applicable

can be safely performed 12 weeks or more after CRT without adversely affecting surgical outcome and survival.[24] This finding supports a more desirable delayed post CRT neck assessment.

Based on our findings showing a pathological rate of residual disease in the neck of 81 % of ycN + patients, a salvage ND should be performed in these patients. In fact, although ND may negatively impact patients' quality of life by exacerbating posttreatment fibrosis of the neck and edema of the upper aerodigestive tract with consequent chronic oropharyngeal dysphagia, salvage ND was shown to improve regional control in patients who did not achieve a CR after organ preservation strategies.[6,16,17,25,26] In ours and in other series, histological analysis of the ND specimen showed the suboptimal positive predictive value of combined physical and imaging assessment (CT or MRI) in the post CRT assessment.[21–27] Despite the growing use of [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) combined with CT scan in HNSCC, its role in post CRT assessment is still controversial. In unselected patients, FDG-PET/CT performed within 8 weeks after completion of CRT, has been shown to have no advantage over the CT scan alone in predicting the need for ND following organ preservation strategies, whereas it may provide benefit when applied in patients who were at elevated risk for treatment failure (patients with HPV-negative tumors, nonoropharyngeal carcinomas, and history of alcohol and tobacco use).[28–30]

With a median follow-up of 28 months, Porceddu et al. observed no nodal failures and 4 distant failures in 41 undissected patients with 12-week FDG-PET-negative and residual CT nodal abnormalities; overall, the positive predictive value for CT was only 14 %.[31] This is in contrast with the rate of concordance between CT nodal abnormalities and findings in ND specimen found in these and other series.[18,21] This may imply that residual VTCs have a low proliferative potential. However, Ganly et al. reported that patients with VTCs in postchemoradiation neck dissection specimens had a poorer outcome compared with patients with no VTCs.[32] These conflicting results suggest more research is needed to better identify VTCs and understand their biology. Furthermore, a longer follow-up is necessary before concluding that radiological findings did not correlate with clinical endpoints.

Among the reasons cited in favor of PND in patients with pretherapy high-volume neck metastases is the particular concern for N3 disease. Some authors, who firmly recommend ND for N2 disease only for residual disease, have called for a more cautionary approach in patients with N3 disease.[15,17–19] Really, there are some factors that may impede us to give strong recommendations for patients with nodes more than 6 cm. First, to create a larger and

more robust sample, in several series evaluating the necessity of PND in clinical complete responders, N2 and N3 patients are often grouped together.[9,13,16,27] Second, N3 patients usually represented a small fraction of patients with advanced neck stage at diagnosis who have a lower probability to achieve a cCR. Nevertheless, when applying contemporary organ preservation strategies involving the concurrent administration of platinum-based chemoradiotherapy without PND, the crude rate of regional failure in initial N3 patients is 7.4 % (95 % CI 3.0 %–17.6 %) (Table 3). Furthermore, the systematic application of PND may represent a futile treatment in N3 patients in which distant failure accounts for the vast majority of recurrences.[13,33,34]

The main limitations of this study include its retrospective nature, the overall small sample size, and the small numbers of individuals submitted to PND, which limits statistically meaningful comparisons between neck management approaches. In addition, prospective randomized trials evaluating the impact of PND in patients submitted to organ preservation strategies are expected to be difficult to accomplish. The consistent recent data from several other series using contemporary multimodality strategies (Table 3) and radiological-based posttherapy assessment contribute to considering PND obsolete. Furthermore, the expected increase in chemoradiosensitive HNSCC due to emerging role of HPV infection in oropharyngeal oncogenesis will result in higher rate of complete remission after organ preservation strategies. In this scenario, an approach advocating systematic PND will add unwarranted morbidity in a growing number of patients.

In conclusion, based on regional control rate and pattern of failure observed in this series, a PND appears not justified in physical and radiological complete responders to platinum-based multidrug IC/CCRT. Conversely, PND should be applied to patients obtaining less than cCR, as a significant proportion of these patients have VTCs on histological examination of the neck specimen.

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