

## REVIEW

# Treatment of advanced neck metastases

## *Il trattamento delle metastasi laterocervicali in stadio avanzato*

G. SPRIANO, R. PELLINI, V. MANCIOCCO, P. RUSCITO

Department of Otolaryngology Head and Neck Surgery, National Cancer Institute "Regina Elena", Rome, Italy

**Key words**

Locally advanced head &amp; neck cancer • Cervical nodal metastases • Neck dissection

**Parole chiave***Carcinoma della testa e del collo localmente avanzato • Metastasi laterocervicali • Svuotamento linfonodale laterocervicale***Summary**

Despite the use of aggressive single or multimodality treatment protocols, patients with advanced cervical metastases, N2 and N3, have a poor prognosis because of their high risk of regional and distal failure. Moreover, N3 class does not allow resectability and curability to be defined. Numerous trials have been carried out in order to improve the oncological outcomes of patients with advanced metastases to the neck using a variety of multimodality therapy. At present, there is a trend toward the use of a definitive radiochemotherapy followed, or not, by neck dissection. In order to offer a panoramic view of the treatment protocols in use, data available in the literature, regarding the management of advanced neck disease using surgery, radiotherapy and chemotherapy, in different associations, have been reviewed and our experience reported. The presence of advanced cervical metastases is a very poor prognostic factor. The combined treatment modality offers better chances of cure than single modality treatment. Surgery followed by radiotherapy or chemo-radiation therapy is an effective and well standardized approach. The use of planned neck dissection following chemoradiation is still debated.

**Riassunto**

*Malgrado l'impiego di protocolli di trattamento monomodali o multimodali particolarmente aggressivi, i pazienti con metastasi laterocervicali in stadio avanzato N2 ed N3, presentano a tuttoggi prognosi severa per l'elevato rischio di recidive locali e/o a distanza. Inoltre la classe N3 non consente di definire un parametro di resecabilità e di curabilità, così come invece avviene nel caso del T4, che è distinto in "a", resecabile, ed in "b", non resecabile e/o non curabile. Per tali ragioni sono stati effettuati diversi studi con l'intento di migliorare i risultati oncologici del trattamento delle metastasi laterocervicali in stadio avanzato per lo più utilizzando protocolli terapeutici multimodali. L'orientamento attuale prevede l'impiego di chemio-radioterapia concomitante con intenti di radicalità, seguita o meno da svuotamento linfonodale laterocervicale. Al fine di fornire una panoramica dei protocolli terapeutici più aggiornati e maggiormente diffusi, sono state passate in rassegna le casistiche più significative reperibili in Letteratura e, a margine, si è presentata la casistica personale. La presenza di metastasi laterocervicali in stadio avanzato costituisce indubbiamente un fattore prognostico fortemente negativo. Allo stato attuale un protocollo terapeutico multimodale sembra offrire le migliori possibilità di controllo della malattia e di guarigione, in rapporto ad un approccio monomodale. In linea generale, la chirurgia con intenti di radicalità seguita da chemio-radioterapia concomitante è attualmente da considerarsi quale opzione terapeutica maggiormente efficace e standardizzata. L'impiego dello svuotamento linfonodale laterocervicale "pianificato" dopo chemio-radioterapia è ancora oggetto di discussione.*

**Introduction**

When cervical metastases are present, the prognosis of patients with head and neck squamous cell carcinoma (SCC) is poor and it is affected by the size, number, level, extra-capsular spread (ECS), resectability as well as by previous treatments<sup>1,2</sup>. The group of "advanced nodal disease" includes N2 and N3 TNM categories, but comprises heterogeneous clinical entities with different prognostic relevance and treated by different strategies<sup>3</sup>. Apart from

the primary tumour located in the thyroid gland, skin and rhino-pharynx, the TNM classification defines N2 categories exclusively by the size and the number of metastatic nodes, taking into account the side, but not the level of metastases. Obviously, a single nodal homo-lateral metastasis of 3.5 cm has a prognostic impact different from contra-lateral multiple large nodes. N3 category is defined only by the size of the lymph node, not considering the presence of other elements. Moreover, the TNM classification does not consider the presence of ECS, which, revealed only

by definitive histo-pathological examination, plays an important role, as prognostic factor, and in the planning of adjuvant therapy<sup>2,4,5</sup>. Finally, the prognostic value of recurrence in the neck (rTNM) differs in relation to the kind of primary treatment (surgery or radiotherapy (RT)).

TNM classification lacks the "a" and "b" subgroups, which are present in T4 head and neck cancers, defining them as resectable (or curable) or not. The major problem of N3 resectability regards the carotid involvement.

Concerning the treatment, combined therapy has demonstrated its superiority in loco-regional control over surgery or RT alone, but the timing of therapy – still remains unclear<sup>1,2,6-9</sup>. The results reported in the literature are usually heterogeneous on account of different selection criteria to enrol the patients and endpoints used by the Authors<sup>6-9</sup>.

The purpose of this study was to analyse the therapeutic protocols employed to treat advanced nodal disease, reviewing the oncological outcomes obtained in our experience and reported in the international literature.

### Material and methods: review of literature and personal experience

In the present study, we have considered the current data available in the literature on the oncological outcomes, concerning the management of advanced neck disease using surgery, RT and chemotherapy in different combinations. Moreover, we report our personal experience regarding a group of patients affected by uncertain resectable and curable neck disease. In detail, we have reviewed the results achieved in our series of 89 N3 patients treated from 1984 to 1998 by surgery, alone or with RT (22 cases); by RT, alone or with chemotherapy (53 cases) and with palliative intention (14 cases).

To define the criteria of resectability and curability related to carotid artery encasement, we reviewed the data from the literature and our experience on a series of 14 patients, that underwent, between 1980 and 2005, radical neck dissection extended to the common carotid artery. Then the data of 11 cases, in which a radical neck dissection with R1 or R2 was performed and followed by brachy-therapy using permanent implants of <sup>125</sup>-Iodine seeds have been examined.

With regard to the effectiveness of planned neck dissection after complete or incomplete response to RT, we discuss the ability of imaging techniques and positron emission tomography (PET) to detect residual disease in a group of N2-N3 patients treated with chemo-radiotherapy followed by neck dissection.

## Discussion

### GENERAL CONSIDERATIONS

Patients with advanced metastatic neck disease have a higher risk both of regional and distant failure, that increases with the volume and the number of the nodes involved<sup>2,10-12</sup>. Although an improvement in the loco-regional control rate has been noted in the last 20 years, this only partially influences the overall survival rates, likely due to the distant metastases, which occur in more than 30% of patients, with more than 3 positive lymph-nodes in the neck<sup>12</sup>. Clark et al. recently reported results on 181 patients with N2-N3 neck disease, who underwent initial neck dissection followed by RT; control of neck disease was obtained in 86% of the cases, but disease specific survival was 39% at 5 years only<sup>8</sup>.

If surgery is used as primary treatment, a radical neck dissection as described by Crile<sup>13</sup> or an extended procedure to non lymphatic involved structures is recommended. When RT is preferred as primary treatment, a total neck irradiation boosted on gross nodal disease will be used. The chemotherapy is usually added as associated treatment. At present, there is no gold-standard therapy for advanced neck metastases, and treatment policies vary in the different Institutions. The comparison of data reported in the literature is quite difficult, because most series include, in the same analysis, patients with N2 and N3 neck metastasis. These categories include a large range of clinical entities with different prognostic implications. Disease control and survival depend not only upon the extent of metastasis dissemination, but also on the treatment used, on the primary extension and on other clinical and pathological variables. Finally, due to the poor prognosis of patients with advanced neck disease, less morbid treatments are often considered in patients with poor performance status. Surgery, irradiation, chemotherapy or combined strategies can be adopted. Most head and neck surgeons<sup>14-16</sup> consider neck dissection followed by post-operative radiation or chemo-radiotherapy as the best therapeutic option.

Regarding the indication for adjuvant treatment after neck dissection, RT is indicated in confirmed pN2 and pN3. Two important randomized trials<sup>17,18</sup>, have demonstrated a statistically significant advantage of concurrent chemo-radiotherapy vs. RT alone, in the case of ECS. Following the publication of results of organ preservation protocols, RT associated with chemotherapy followed or not by neck dissection is used as a valid therapeutic option in patients with advanced head and neck tumour. Moreover, combined-modality therapy has been demonstrated to be superior in terms of local control compared to surgery or RT alone<sup>9,19-21</sup>.

### ESCLUSIVE RADIOTHERAPY OR CHEMORADIOTHERAPY

Advanced neck metastases, treated exclusively with RT, have a low rate of disease control associated with a high rate of recurrence, independently of the site of the primary tumour and the RT dose. Narayan et al., on a series of 52 patients with neck nodal metastases > 30 mm, noted that after exclusive RT, residual disease was present in the neck in 24 cases (46%)<sup>9</sup>. Carvalho et al., on a series of 137 N3 patients treated with RT alone (mean dose 60 Gy), achieved control of neck disease in 16.1% of patients, with salvage surgery not being feasible in any of these cases<sup>7</sup>. Moreover, as noted by Mendenhall et al.<sup>22</sup>, the efficacy of RT alone in the treatment of nodal disease decreases with the increasing volume of the metastases, with local control of the disease within 3 years of 0% for nodal disease > 7 cm. The association of chemotherapy (sequential or concurrent) significantly increases loco-regional control and survival. Brizel<sup>23</sup> compared the results obtained in two groups of patients with advanced disease using hyperfractionated RT alone or RT associated with chemotherapy; overall survival at 3 years was significantly better in the group on combined therapy (55% vs. 34%). Similarly, Puc et al.<sup>24</sup> in 48 N2-N3 patients, observed that the association of cisplatin based chemotherapy and hyperfractionated RT leads to complete clinical response in 60% of cases and complete histological response in 45%, following neck dissection (31/48 patients). The 4-year disease-specific survival rate, in N3, was 39%.

### INTRA-ARTERIAL CHEMORADIATION (RADPLAT)

Among the various therapeutic regimens proposed for the treatment of advanced neck disease, some Authors studied the use of an intra-arterial chemoradiation protocol, known as RADPLAT. Robbins et al.<sup>25</sup> reported the results in 52 patients with N2/N3 disease involving 60 necks treated with intra-arterial cisplatin chemotherapy combined with systemic chemo-neutralization. Cisplatin (150 mg/m<sup>2</sup> weekly for 4 weeks) was rapidly infused (3 to 5 min.) in the dominant blood supply of the targeted tumour. Conventional external beam radiation was delivered in a daily fraction to a total dose of 68/74 Gy. The chemotherapy infusion was given on days 1, 8, 15 and 22 of RT. Of the 56 evaluable necks, a clinical complete response was achieved in 33 (59%). With the association of planned selective neck dissection performed in 35 necks the rate of loco-regional disease control achieved 77%. Overall and disease-specific survival at 3 years were 32% and 45%, respectively. Ahmed et al.<sup>19</sup> studied 26 patients with N3 neck metastases who were treated with intra-arterial chemotherapy and RT. The partial response rate was 81% (21/26 cases); but the clinical com-

plete response was obtained only in 4 out of the 26 patients (15%); 19 patients underwent salvage neck dissection and loco-regional control at 3 years was 67%. In conclusion, targeted chemo-radiation with the use of intra-arterial supra-dose cisplatin and concomitant radiation therapy is effective for controlling regional disease, but in most cases the association of neck dissection is necessary to improve loco-regional control.

### SURGERY

Surgery alone in the management of advanced neck disease is marginally effective. Results of surgery alone are rarely reported in the recent literature because, in most of the series, surgery is followed by radio- or chemo-radiotherapy. Stell et al.<sup>26</sup> reported the results of a retrospective study on 139 patients with fixed lymph-node; only 23 selected cases underwent surgery alone, achieving 52% of local control but a 5-year survival of only 15%. On the other hand, 78 patients were considered incurable and 37 were treated with radiation alone.

The small series in the literature treated with neck dissection alone, comprised patients, that were also unable to tolerate adjuvant RT or chemotherapy, thus making the results inaccurate and fragmentary<sup>8,15</sup>.

### SURGERY AND CHEMO-RADIOTHERAPY

Surgery followed by radiation or chemo-radiation is a well established strategy of cure for advanced but resectable neck disease; in well-determined circumstances, such as small primary tumours with huge cervical metastases, the initial surgical management may focus treatment on the neck only, leaving the primary tumour for subsequent RT treatment, with the intent to minimize morbidity. Smeele et al.<sup>14</sup> reported on 37 patients (most primary oro/hypopharynx tumours) with N2-N3 neck disease, treated with surgery followed by chemo-radiotherapy. Five patients were excluded from the analysis because of incomplete treatment, in the remaining 32 patients the overall loco-regional control rate was 43% at 2 years, with an incidence of distant metastases of 31% (10/32 patients). Byers et al.<sup>15</sup> reported on a series of 35 patients treated with neck dissection followed by RT. For the subgroup of patients with small primary T1-T2 and neck nodes > 3 cm, survival at 5 years was 55% with regional (neck) failure occurring in 11% (4 out of 35 patients). Likewise, Allal et al.<sup>16</sup> retrospectively evaluated 24 patients (group 1) with pharyngeal carcinoma and N2-N3 neck disease, treated by neck dissection followed by RT and 17 patients (group 2) treated by radical RT alone. Three-year actuarial loco-regional control was 73% and 55% for groups 1 and 2, respectively, (p = 0.52). The corresponding 3-year actuarial overall survival rates were 37% and 50%, respectively, (p = 0.42). It should be noted that the data are partially altered by the fact

that chemotherapy was delivered to 6 patients in group 1 and 8 in group 2. Clark et al.<sup>8</sup> analysed 181 patients with advanced neck metastases treated by neck dissection followed by RT in 82% of cases. Ipsilateral control in the treated neck was achieved in 86% of cases, but disease-specific survival, at 5 years, was only 39%. The Authors, with the use of multivariate analysis, identified, in macroscopic ECS and N2c neck disease, adverse prognostic factors for survival.

In conclusion, neck dissection for advanced neck disease followed by planned RT offers good local control of the disease, but the poor survival rate indicates that adjuvant therapeutic strategies need to be considered because the incidence of distant failure, as well as other causes of death, are frequent.

With regard to our experience on 89 patients with N3 disease, we have observed an overall survival rate, at 3 years, of 7.5% in the group of 53 patients submitted to exclusive RT or chemo-radiation therapy; 30% for the 22 patients treated by surgery and RT. The selection of the candidate to the two different options does not allow comparison of the results. Overall, 14 patients were considered incurable and treated with palliation alone, stressing the opportunity to introduce, in the classification, a parameter of selection in order to assess the curability and resectability.

#### CHEMO-RADIATION AND PLANNED NECK DISSECTION

Most mucosal head and neck tumours, especially if in the initial stage and in a specific site such as the pharynx, respond well to RT alone. On the other hand, when high volume neck metastases are present, the choice to manage the neck by chemo-radiotherapy must be based on the fact that high volume neck metastases are rarely responsive to RT alone, whereas the concurrent chemo-radiation therapy has been shown to be more effective<sup>27</sup>; moreover, the radiobiological sensitivity should be better in primary intention<sup>28</sup>. Evaluation of the irradiated neck is often imprecise due to post-treatment fibrosis. The possi-

bility of residual clinical neck mass that may possibly harbour viable cancer and the possibility of the presence of residual vital cells even in the case of complete clinical remission makes it difficult to decide whether or not a planned neck dissection should be carried out.

On the basis of these considerations, the current opinion is that planned neck dissection following definitive RT or radiotherapy plus chemotherapy for bulky clinical neck disease, regardless of the clinical or radiographic response to treatment, improves the prognosis. This finding is supported by the study of Parsons et al.<sup>29</sup> who recently reported improvement of neck control rates in patients with N2-N3 disease treated with RT and planned neck dissection vs. RT alone and by the study of McHam et al.<sup>6</sup>, that demonstrated 25% of residual pathologic evidence of neck disease in N2-N3 patients that completely responded to chemo-radiation therapy. On the other hand, there are the patients with incomplete clinical response to chemo-radiation therapy that only in 39% of cases show residual tumour in the neck at surgery<sup>6</sup>. For these reasons, many important oncologic Institutes in the world, tend to avoid neck dissection in patients with a complete clinical response. Table I outlines the indication to neck dissection after initial chemo-radiation reported in the literature. It is, therefore, necessary to clarify the role of planned neck dissection in relation to concomitant chemo-radiation protocols and the selection criteria that will identify patients who will benefit from neck dissection from those who will not.

At present, none of the available diagnostic techniques can identify, in all cases, the presence of residual node disease. The main limit of traditional imaging techniques is the difficult to clearly distinguish viable residual tumour from scar tissue or necrosis. Computed tomography (CT) has a false positive error rate ranging from 7% to 30% when considering pathologic nodes > 1.5 cm and the use of magnetic resonance imaging (MRI) added only a

**Table I.** Recommended Planned Neck Dissection after CT/RT (Review of the Literature).

Always (ref. no.)	If partial or non responder (ref. no.)
Leon X, et al. <i>Eur Arch Otolaryngol</i> 2000 (41)	Johnson CR, et al. <i>Radiat Oncol Invest</i> 1998 (48)
Stenson KM, et al. <i>Arch Otolaryngol Head Neck Surg</i> 2000 (35)	Narayan K, et al. <i>Head Neck</i> 1999 (9)
McHam SA, et al. <i>Head Neck</i> 2003 (6)	Weisman RA, et al. <i>Laryngoscope</i> 1998 (49)
Argiris A, et al. <i>Head Neck</i> 2004 (42)	Porceddu S, et al. <i>Head Neck</i> 2005 (32)
Garg M, et al. <i>Curr Treat Options Oncol</i> 2004 (43)	Yao M, et al. <i>Int J Rad Oncol Biol Phys</i> 2005 (31)
Wang SJ, et al. <i>Laryngoscope</i> 2000 (44)	Garden AS, et al. <i>J Clin Oncol</i> 1999 (50)
Brizel DM, et al. <i>Int J Radiat Oncol Biol Phys</i> 2004 (45)	Corry J, et al. <i>Radiother Oncol</i> 2000 (51)
Robbins KT, et al. <i>Arch Otolaryngol Head Neck Surg</i> 1999 (25)	
Lavertu P, et al. <i>Head Neck</i> 1997 (46)	
Wolf GT, et al. <i>Laryngoscope</i> 1992 (47)	

slight improvement in diagnostic accuracy. An interesting paper from Ojiiri et al. showed a negative predicting value (NPV) of 100% using the combination of size (< 15 mm), free of focal defects and ECS negative at CT imaging<sup>30</sup>.

In the last few years, PET with 18-fluoro-deoxyglucose, based on the high uptake of glucose in the tumour mass compared to the surrounding tissue has been introduced in order to increase the accuracy of post-therapy staging. PET-CT fusion scan combines the metabolic information obtained from PET with anatomic information obtained with CT, hopefully amplifying the ability to detect the presence of residual disease. Yao et al.<sup>31</sup> studied a group of 41 patients with regionally advanced disease, treated with RT with or without chemotherapy, considering a cut off of SUV = 3 (standardized uptake value). The NPV was 100%, positive prediction value (PPV) 80%. Porceddu et al.<sup>32</sup> reported a PPV of 71% and NPV of 97%. Whereas, Gourin et al.<sup>33</sup> recently studied, with PET-CT, a group of 17 N2-N3 patients complete responders to chemo-radiation therapy. Only 2 out of 11 (18.2%) patients with positive PET-CT presented residual carcinoma at pathological examination after neck dissection and 3 out of 6 (50%) PET-CT negative patients were completely free of the disease in the neck. McColium et al. reported a sensitivity of 67% and specificity of 53%, an overall accuracy of 58%, a PPV of 46% and NPV of 73%<sup>34</sup>. These differences reported in the diagnostic accuracy of PET-CT show that this technique has not yet reached sufficient accuracy to select whether or not a planned neck dissection is indicated.

We studied a group of 12 patients with oropharyngeal cancer and N2 metastatic nodal disease treated with primary chemo-radiation therapy followed by planned neck dissection regardless of the response of the neck disease. We evaluated the clinical response by PET-CT, MRI and ultrasonography (US) 12 weeks after the end of chemo-radiation therapy. Results have been correlated to pathological reports following neck dissection. The NPV of PET/CT, MRI and US was 60%, 80%, 83%, respectively. The PPV was 100%, 71% and 83%, respectively. We have concluded that none of the single modalities is able to correctly detect the status of the node, but the combination of all four diagnostic modalities (clinical assessment, PET, MRI and US) showing a negative neck is associated with a NPV of 100%. This approach is more expensive, but effective.

Regarding the type of procedure, a radical neck dissection according to Crile, is considered the standard treatment, even if recently a less invasive procedure, namely, selective neck dissection has been proposed in order to minimize neck dissection morbidity, sparing marginal node levels, where micro-metastases,

when present, were probably eliminated by the initial chemo-radiation therapy<sup>25 35</sup>.

#### EXTENDED SURGERY

From a surgical viewpoint, un-resectability is defined by invasion of cervical non-lymphatic structures not amenable to resection; these structures include the skull base, vertebrae and the common and/or internal carotid artery. Fixation of the mass to the surrounding structures, such as the presence of cranial nerve palsies, is a clinical indicator of extra-nodal extension, but it is not an absolute criteria for unresectability or non-curability. A conflict exists between what it would take to resect the metastasis vs. the impact of such resection could have on the patient's quality of life; although it may be possible to achieve a total macroscopic resection, morbidity may be questionable. These decisions must be considered individually and the surgeon has to be able to recognise curable patients and resectable disease.

Pre-operative imaging options (CT, MRI) commonly used to evaluate the extension of the disease to surrounding structures, have a good NPV but a poor PPV. Regarding the carotid artery encasement, the share of vessel encircled by the tumour is used as an indicator of vessel invasion. In the case of more than 180° of encirclement evident at CT, the sensitivity of the method in detecting vascular invasion is as low as 18.5%, but it is a good indicator of poor clinical outcome, the overall survival rate is 8.3% at 2 years<sup>36 37</sup>. The maximum accuracy is obtained when different parameters are considered, particularly compression and deformation of the artery and partial fat or fascia deletion between tumour and vessel (84.1%)<sup>38</sup>. Whereas, with regard to MRI, the single criterion of involvement of 270° or more of the circumference of the carotid artery accurately predicts the surgeon's inability to peel the tumour off the carotid artery in 100% of the cases, as reported by Yousem et al.<sup>39</sup>. Thus in cases of encirclement of the carotid artery of less than 270°, the ultimate resectability of the mass can only be determined at the time of surgery.

Certainly, the carotid artery is the most difficult structure to manage in advanced cervical disease. Usually, it is the last structure to be sacrificed during extended radical neck dissection, and vessel resection is performed after complete exploration of the neck in order to be sure regarding complete removal of the tumour. If the involved carotid cannot be sacrificed because it is impossible to reconstruct the vessel, in the case of insufficient cerebral collateral circulation, subtotal resection, associated with Intra-operative Radiotherapy (IORT) or brachitherapy have been proposed as an acceptable alternative to treat the tissue at risk of microscopic disease af-

**Table II.** Neurologic sequelae and mortality of carotid artery resection (review of literature and personal experience).

Author (Ref.)	Cases NO.	Revascularization %	Stroke %	Mortality %
Freeman SB, et al. Laryngoscope 2004 (52)	58	80 Yes	20	3
Wright JC, et al. J Vasc Surg 1996 (53)	20	20 No Yes	20 10	0
Meleca RJ, et al. Arch Otol H&N Surg 1994 (54)	20	8 Yes 12 No	13 58	ND
Jacobs JR, et al. Am J Otolaryngol 2001 (55)	18	Yes	0	0
Katsuno S, et al. Laryngoscope 1997 (56)	9	Yes	0	11
Brennan JA, et al. Laryngoscope 1994 (57)	7	No	2	29
Feiz-Erfan I, et al. Neurosurg Focus 2003 (58)	5	Yes	1	20
Muhm M, et al. Acta Otolaryngol 2002 (59)	5	Yes	0	15
Spriano G, et al. (in press)	14	4 Yes 10 No	0	0

ter cancer extirpation<sup>40</sup>. In the case of definitive ligation of the carotid artery, there is a high risk of cerebrovascular complications, that may occur immediately, because of inadequate perfusion of the brain, or during the post-operative period because of distal thrombus formation and embolism. Table II outlines the neurologic sequelae of carotid artery resection described by different Authors. It is mandatory to pre-operatively identify the patients at risk for neurologic sequelae, evaluating the collateral cerebral blood flow through the balloon occlusion test. The cerebral perfusion and the patency of the carotid artery are assessed pre-operatively; then a balloon is inflated inside the carotid stopping the blood flow for 20 minutes, during this period, the patient is monitored with regard to neurologic compromise and cerebral perfusion is tested with Single Photon Emission Computed Tomography (SPECT). The sensitivity of the test can be improved by inducing a hypotensive status. In the case of patients at higher risk of cerebral ischaemia, the involved artery can be by-passed with a temporary shunt that ensures cerebral perfusion during the placement of a graft (vein or alloplastic materials). Vascular reconstruction is suitable also in patients with safe collateral cerebral circulation, not only because the graft re-establishes cerebral blood flow, but it minimizes the risk of clot and thrombus propagation due to stasis of the blood. Coverage of the reconstructed artery by pedicled *pectoralis major* flap is reliable especially when post-operative RT on the neck is scheduled or has already been delivered. Even in

the case of carotid reconstruction, every effort must be made to maintain blood pressure within the normal range during surgery as well as in the post-operative period<sup>36</sup>.

Our series refers to 14 cases, who underwent radical neck dissection extended to carotid artery resection, on account of encasement. In 10 patients, the artery has been resected without reconstruction, in 2 cases, the carotid trunk has been reconstructed by means of an alloplastic prosthesis and, in 2 cases, a patch has been sutured, after partial removal of the carotid wall, at the level of the bifurcation. Even in the 4 cases, in which reconstruction was effected, temporary interruption of the vascular flow occurred, no strokes or peri-operative mortality were observed. All patients but one, affected by nodal metastasis from medullary carcinoma of the thyroid gland, died. One patient died after 3 years due to heart failure without disease.

Cervical skin invasion by extended cervical metastases is quite frequent. Large amounts of skin can be sacrificed without any functional impairment. Only rarely, is direct closure possible. The use of a free flap is not always possible since it increases the complexity of the procedure in patients with a poor chance of cure and because neck vessels are rarely available for micro-anastomosis. It is preferable to use a pedicled flap, particularly *pectoralis major*, that offers a large portion of skin paddle associated with vital muscle that can be used to protect the carotid artery and to fill the dissected neck.

If one or more cranial nerves are paralysed pre-operatively, sacrifice is made without direct inspection. In the case of intra-operative evidence of nerve invasion, the nerve can be resected.

Resection of multiple cranial nerves is associated, especially in the elderly, with a high rate of post-operative dysphagia and lung complications. Invasion of the sympathetic cervical chain and its surgical removal will determine Bernard Horner Syndrome.

Excision of the splenius and *levator scapulae* muscles can be performed in the case of direct invasion by the tumour. This sacrifice will usually determine shoulder morbidity especially when, as often occurs, innervation of the trapezius muscle is also sacrificed. Bony structures such as mastoid, clavicle, vertebra and mandible can be invaded by the tumour. Mastoid and clavicle can be resected without reconstruction. Vertebral infiltration is a dramatic situation not amenable to surgical treatment. Management of mandible invasion can be resolved by marginal or segmental resection. Marginal inferior mandibulectomy does not require any specific reconstruction. Segmental resection of the mandible might require some type of reconstruction. Fibula or iliac crest free flaps are the best options, but their use is limited to very selected cases, on account of the complexity of the procedure in patients with poor prognosis and the paucity of suitable recipient vessels in the dissected neck.

Pre-operative assessment of patients must take into consideration certain parameters to select candidates for this type of surgery. Generally, SCC has a better prognosis than other histological conditions; skin and carotid artery involvement is worse than infiltration of others structures of the neck; a bilateral or contralateral node disease, as well as para-pharyngeal mass, is related to a poorer prognosis; involvement of lymph-nodes located at lower levels (IV, V, VI) is another unfavourable situation compared to nodes located at upper levels (I, II, III).

A score system based not only on patients characteristics, such as age, performance status, mortality risk, neurologic risk and quality of life, but also on tumour characteristics, such as previous treatment, probability of leaving residual disease, and survival at 3 years, would be useful to select candidates for aggressive surgery.

Considering the high impact on the future quality of life of the patient undergoing this type of surgery which is often associated with adjuvant treatment, the decision on the neck must be associated with evaluation of the status of the primary lesion and with a meticulous search for distant metastases and surgery on the neck can be performed only when a plan of treatment has been made to obtain a reasonable chance of cure. With the development of recon-

structive techniques, the word "inoperable" has become obsolete, everything is always operable, but operable does not mean curable. One of the most difficult situations for a surgeon is to decide when a patient has no chance of cure, but technical demonstration of surgical expertise, when there is no benefit for the patient, should be avoided.

## RECURRENCE

One peculiar situation concerns patients with recurrence in the neck. Generally, very poor prognosis limits the treatment to a palliative cure, but some differences exist, especially regarding the initial treatment and the stage of recurrence, when detected. Patients with recurrence after initial RT treatment should not be considered for re-irradiation, that is rarely possible; a radical neck dissection offers some chance of cure. With regard to this situation, we have started a phase I study in which an extra dose (usually 12 Gy) of IORT is given during surgery; 25 patients have been thus treated, so far, but the follow-up is, as yet, too short to define the oncological value.

The worst situation occurs in the case of recurrence in patients initially treated with surgery and RT. Evaluation of the neck is difficult on account of the scar and radio-induced fibrosis, thus recurrence is generally detected late, moreover, salvage surgery is associated with an increased risk of post-operative complications and poor oncological outcomes. We have treated 11 consecutive patients presenting recurrence in the neck and controlled diseases in the primary tumour, using brachi-therapy by means of <sup>125</sup>-iodine seeds: 4 cases were recurrences following surgery and RT; 7 cases presented a rN3 following radiation ± chemotherapy, in which radicality could not be macroscopically achieved by radical neck dissection. All 4 patients with recurrence, after surgery, died with disease in the neck; all 7 patients with recurrence following RT died but 4 out of 7 on account of M1 without disease in the neck. In any case, repeat treatment, on the neck, has to be considered an exception; the majority of recurrences in the neck are candidate for palliative procedures.

## Conclusion

The treatment of choice for advanced neck disease is multimodal: surgery followed by chemo-radiotherapy for SCC arising from the skin, salivary glands, lip and oral cavity; for most pharyngeal and laryngeal carcinomas with advanced cervical nodal disease, neck dissection is part of the treatment and can be performed after associated chemo-radiation.

Planned neck dissection is still controversial, until imaging techniques are able to select the right can-

didate that will truly benefit because of residual disease.

Involvement of non-lymphatic structures of the neck, strongly common carotid artery, need meticulous

evaluation both of the patient and disease to be submitted to aggressive surgery.

Recurrence in the neck, usually, has to be considered an incurable disease.

## References

- <sup>1</sup> Shah JP. *Cervical lymph node metastases – diagnostic, therapeutic and prognostic implications*. *Oncology* 1990;1:61-9.
- <sup>2</sup> O'Brien CJ, Smith JW, Soung SJ, Urist MM, Maddox WA. *Neck dissection with and without radiotherapy: prognostic factors, patterns of recurrence and survival*. *Am J Surg* 1986;152:456-63.
- <sup>3</sup> Sobin LH, Wittekind CH. *TNM Classification of Malignant Tumours*. 6th edn. New York, NY, USA: Wiley; 2002.
- <sup>4</sup> Johnson JT, Barnes EL, Myers EN, Schramm VL Jr, Borodovitz D, Sigler BA. *The extracapsular spread of tumour in cervical node metastasis*. *Arch Otolaryngol* 1981;107:725-9.
- <sup>5</sup> Myers EN, Greenberg JS, Mo V, Roberts D. *Extracapsular spread. A significant predictor of treatment failure in patients with squamous cell carcinoma of the tongue*. *Cancer* 2001;92:3030-6.
- <sup>6</sup> McHam SA, Aldestein DJ, Rybicki LA, Lavertu P, Esclamado RM, Wood BG, et al. *Who merits a neck dissection after definitive chemoradiotherapy for N2-N3 squamous cell head and neck cancer?* *Head Neck* 2003;25:791-8.
- <sup>7</sup> Carvalho AL, Kowalski LP, Agra IMG, Doutes E, Campos OD, Pellizzon AC. *Treatment results on advanced neck metastases (N3) from head and neck squamous carcinoma*. *Otolaryngol Head Neck Surg* 2005;132:862-8.
- <sup>8</sup> Clark J, Li W, Smith G, Shannon K, Clifford A, McNeil E, et al. *Outcome and treatment for advanced cervical metastatic squamous cell carcinoma*. *Head Neck* 2005;27:87-94.
- <sup>9</sup> Narayan K, Crane CH, Kleid S, Hughes PG, Peters LJ. *Planned neck dissection as an adjunct to the management of patients with advanced neck disease treated with definitive radiotherapy: for some or for all?* *Head Neck* 1999;21:606-13.
- <sup>10</sup> Kalnins IK, Leonard AG, Sako K, Razack MS, Shedd DP. *Correlation between prognosis and degree of lymph node involvement in carcinoma of the oral cavity*. *Am J Surg* 1977;134:450-4.
- <sup>11</sup> Snow GB, Annyas AA, van Slooten EA, Bartelink H, Hart AA. *Prognostic factors of neck node metastases*. *Clin Otolaryngol* 1982;7:85-92.
- <sup>12</sup> Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. *Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma*. *Cancer* 1993;71:452-6.
- <sup>13</sup> Crile G. *Landmark article Dec 1, 1906: Excision of cancer of the head and neck. With special reference to the plan of dissection based on one hundred and thirty-two operations*. *JAMA* 1987;11:258:3286-93.
- <sup>14</sup> Smelee LE, Leemans CR, Colin BA, Reid CB, Tiwari R, Snow GB. *Neck dissection for advanced lymph node metastasis before definitive radiotherapy for primary carcinoma of the head and neck*. *Laryngoscope* 2000;110:1210-4.
- <sup>15</sup> Byers RM, Clayman GL, Guillaumondequi OM, Peters LJ, Goepfert H. *Resection of advanced cervical metastasis prior to definitive radiotherapy for primary squamous carcinomas of the upper aerodigestive tract*. *Head Neck* 1992;14:133-8.
- <sup>16</sup> Allal AS, Dulguerov P, Bieri S, Lehmann W, Kurtz JM. *A conservation approach to pharyngeal carcinoma with advanced neck disease: optimizing neck management*. *Head Neck* 1999;21:217-22.
- <sup>17</sup> Bernier J, Domezge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al.; European Organization for Research and Treatment of Cancer Trial 22931. *Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer*. *N Engl J Med* 2004;350:1945-52.
- <sup>18</sup> Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Radiation Therapy Oncology Group 9501/Intergroup. *Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck*. *N Engl J Med* 2004;350:1937-44.
- <sup>19</sup> Ahmed KA, Robbins KT, Wong F, Salazar JE. *Efficacy of concomitant chemoradiation and surgical salvage for N3 nodal disease associated with upper aerodigestive tract carcinoma*. *Laryngoscope* 2000;110:1789-93.
- <sup>20</sup> Mendenhall WM, Million RR, Cassisi NJ. *Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes*. *Int J Radiat Oncol Biol Phys* 1986;12:733-40.
- <sup>21</sup> Kramer S, Gelber RD, Snow JB, Marcial VA, Lowry LD, Davis LW, et al. *Combined radiation therapy and surgery in the management of advanced head and neck cancer: final report study 73-03 of the Radiation Therapy Oncology Group*. *Head Neck Surg* 1987;10:19-30.
- <sup>22</sup> Mendenhall WM, Million RR, Bova FJ. *Analysis of time – dose factors in clinically positive neck nodes treated with irradiation alone in squamous cell carcinoma of the head and neck*. *Int J Radiat Oncol Biol Phys* 1984;10:639-43.
- <sup>23</sup> Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. *Hyper fractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer*. *N Engl J Med* 1998;338:1798-804.
- <sup>24</sup> Puc MM, Chrzanowski FA Jr, Tran HS, Liu L, Glicksman AS, Landman C, et al. *Preoperative chemotherapy-sensitized radiation therapy for cervical metastases in head and neck cancer*. *Arch Otolaryngol Head Neck Surg* 2000;126:337-42.
- <sup>25</sup> Robbins KT, Wong FS, Kumar P, Hartsell WF, Vieira F, Mullins B, et al. *Efficacy of targeted chemoradiation and planned selective neck dissection to control bulky nodal disease in advanced head and neck cancer*. *Arch Otolaryngol Head Neck Surg* 1999;125:670-5.
- <sup>26</sup> Stell PM, Dalby JE, Singh SD, Taylor W. *The fixed cervical lymph node*. *Cancer* 1984;53:336-41.
- <sup>27</sup> Bourhis J, Guigay J, Temam S, Pignon JP. *Chemo-radiotherapy in head and neck cancer*. *Ann Oncol* 2006;17:39-41.

- 28 Rosenberg SA. *Principles and practice of the biologic therapy of cancer*. 3<sup>rd</sup> Edn. New York: Lippincott C 2000.
- 29 Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. *Twice-a-day radiotherapy for squamous cell carcinoma of the head and neck: the University of Florida experience*. *Head Neck* 1993;15:87-96.
- 30 Ojiiri H, Mendenhall WM, Stringer SP. *Post-RT CT results as a predictive model for the necessity of planned post-RT neck dissection in patients with cervical metastatic disease from squamous cell carcinoma*. *Int J Radiat Oncol Biol Phys* 2002;52:420-8.
- 31 Yao M, Smith RB, Graham MM, Hoffman HT, Tan H, Funk GF, et al. *The role of FDG PET in management of neck metastasis from head-and-neck cancer after definitive radiation treatment*. *Int J Radiat Oncol Biol Phys* 2005;63:991-9.
- 32 Porceddu SV, Jarmolowski E, Hicks RJ, Ware R, Weih L, Rischin D, et al. *Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo)radiotherapy in head and neck cancer*. *Head Neck* 2005;27:175-81.
- 33 Gourin CG, Williams HT, Seabolt WN, Herdman AV, Howington JW, Terris DJ. *Utility of positron emission tomography-computed tomography in identification of residual nodal disease after chemoradiation for advanced head and neck cancer*. *Laryngoscope* 2006;116:705-10.
- 34 McCollum AD, Burrell SC, Haddad RI, Norris CM, Tishler RB, Case MA, et al. *Positron emission tomography with 18F-fluorodeoxyglucose to predict pathologic response after induction chemotherapy and definitive chemoradiotherapy in head and neck cancer*. *Head Neck* 2004;26:890-6.
- 35 Stenson KM, Haraf DJ, Pelzer H, Recant W, Kies MS, Weichselbaum RR, et al. *The role of cervical lymphadenectomy after aggressive concomitant chemoradiotherapy: the feasibility of selective neck dissection*. *Arch Otolaryngol Head Neck Surg* 2000;126:950-6.
- 36 Yoo GH, Hocwald E, Korkmaz H, Du W, Logani S, Kelly JK, et al. *Assessment of carotid artery invasion in patients with head and neck cancer*. *Laryngoscope* 2000;110:386-90.
- 37 Yu Q, Wang P, Shi H, Luo J. *Carotid artery and jugular vein invasion of oral maxillo-facial and neck malignant tumours: diagnostic value of computed tomography*. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;96:368-72.
- 38 Freeman SB. *Advanced cervical metastasis involving the carotid artery*. *Curr Opin Otolaryngol Head Neck Surg* 2005;13:107-11.
- 39 Yousem DM, Hatabu H, Hurst RW, Seigerman HM, Montone KT, Weinstein GS, et al. *Carotid artery invasion by head and neck masses: prediction with MR imaging*. *Radiology* 1995;195:715-20.
- 40 Pinheiro AD, Foote RL, McCaffrey TV, Kasperbauer JL, Bonner JA, Olsen KD, et al. *Intraoperative radiotherapy for head and neck and skull base cancer*. *Head Neck* 2003;25:217-25.
- 41 Leon X, Quer M, Orus C, de Dios E, Recher K. *Treatment of neck nodes after induction chemotherapy in patients with primary advanced tumours*. *Eur Arch Otorhinolaryngol* 2000;257:521-5.
- 42 Argiris A, Stenson KM, Brockstein BE, Mittal BB, Pelzer H, Kies MS, et al. *Neck dissection in the combined-modal-ity therapy of patients with locoregionally advanced head and neck cancer*. *Head Neck* 2004;26:447-55.
- 43 Garg M, Beitler JJ. *Controversies in management of the neck in head and neck cancer*. *Curr Treat Options Oncol* 2004;5:35-40.
- 44 Wang SJ, Wang MB, Yip H, Calcaterra TC. *Combined radiotherapy with planned neck dissection for small head and neck cancers with advanced cervical metastases*. *Laryngoscope* 2000;110:1794-7.
- 45 Brizel DM, Prosnitz RG, Hunter S, Fisher SR, Clough RL, Downey MA, et al. *Necessity for adjuvant neck dissection in setting of concurrent chemoradiation for advanced head-and-neck cancer*. *Int J Radiat Oncol Biol Phys* 2004;58:1418-23.
- 46 Lavertu P, Adelstein DJ, Saxton JP, Secic M, Wanamaker JR, Eliachar I, et al. *Management of the neck in a randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer*. *Head Neck* 1997;19:559-66.
- 47 Wolf GT, Fisher SG. *Effectiveness of salvage neck dissection for advanced regional metastases when induction chemotherapy and radiation are used for organ preservation*. *Laryngoscope* 1992;102:934-9.
- 48 Johnson CR, Silverman LN, Clay LB, Schmidt-Ullrich R. *Radiotherapeutic management of bulky cervical lymphadenopathy in squamous cell carcinoma of the head and neck: is postradiotherapy neck dissection necessary?* *Radiat Oncol Invest* 1998;6:52-7.
- 49 Weisman RA, Christen RD, Jones VE, Kerber CW, Seagren SL, Orloff LA, et al. *Observations on control of N2 and N3 neck disease in squamous cell carcinoma of the head and neck by intra-arterial chemoradiation*. *Laryngoscope* 1998;108:800-5.
- 50 Garden AS, Glisson BS, Ang KK, Morrison WH, Lippman SM, Byers RM, et al. *Phase I/II trial of radiation with chemotherapy "boost" for advanced squamous cell carcinomas of the head and neck: toxicities and responses*. *J Clin Oncol* 1999;17:2390-5.
- 51 Corry J, Rischin D, Smith JG, D'Costa IA, Huges PG, Sexton MA, et al. *Radiation with concurrent late chemotherapy intensification ('chemoboost') for locally advanced head and neck cancer*. *Radiation Oncol* 2000;54:123-7.
- 52 Freeman SB, Hamaker RC, Borrowdale RB, Huntley TC. *Management of neck metastasis with carotid artery involvement*. *Laryngoscope* 2004;114:20-4.
- 53 Wright JG, Nicholson R, Schuller DE, Smead WL. *Resection of the internal carotid artery and replacement with greater saphenous vein: a safe procedure for en bloc cancer resections with carotid involvement*. *J Vasc Surg* 1996;23:775-80.
- 54 Meleca RJ, Marks SC. *Carotid artery resection for cancer of the head and neck*. *Arch Otolaryngol Head Neck Surg* 1994;120:974-8.
- 55 Jacobs JR, Korkmaz H, Marks SC, Kline R, Berguer R. *One stage carotid artery resection: reconstruction in irradiated head and neck carcinoma*. *Am J Otolaryngol* 2001;22:167-71.
- 56 Katsuno S, Ishiyama T, Sakaguchi M, Takemae H. *Carotid resection and reconstruction for advanced cervical cancer*. *Laryngoscope* 1997;107:661-4.

- <sup>57</sup> Brennan JA, Jafek BW. *Elective carotid artery resection for advanced squamous cell carcinoma of the neck*. Laryngoscope 1994;104:259-63.
- <sup>58</sup> Feiz-Erfan I, Han PP, Spetzler RF, Lanzino G, Ferreira MA, Gonzalez LF, et al. *Salvage of advanced squamous cell carcinomas of the head and neck: internal carotid artery sacrifice and extracranial-intracranial revascularization*. Neurosurg Focus 2003;14:e6.
- <sup>59</sup> Muhm M, Grasl MCh, Burian M, Exadaktylos A, Staudacher M, Polterauer P. *Carotid resection and reconstruction for locally advanced head and neck tumours*. Acta Otolaryngol 2002;122:561-4.

■ Received: September 26, 2006  
Accepted: October 15, 2006

■ Address for correspondence: Dr. G. Spriano, Dipartimento di Otorinolaringoiatria e Chirurgia Testa e Collo, Istituto Nazionale "Regina Elena", via Chianesi 53, 00144 Roma, Italy. E-mail: orl@ifso.it