

Advanced head and neck treatment. Neoadjuvantly, concomitantly or surgery?

Tratamiento del cáncer avanzado de cabeza y cuello. ¿Neoadyuvancia, concomitancia o cirugía?

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Standard and historical treatment of locally advanced squamous cell carcinoma originating in the mucous membranes of the head and neck has been surgical resection followed by radiotherapy. Only patients at initial stages can receive a single therapeutic variety, either surgical resection or exclusive radiation therapy, with similar results.

Nevertheless, survival of patients with this neoplasm has not improved over the years. To improve it and increase locoregional control, reduce morbidity and preserve organs, specifically the larynx, chemotherapy has been introduced into the therapeutic armamentarium for this neoplasm.

There are still controversies, discussions and doubts¹ that often lead to inappropriate treatment regarding chemotherapy use and indications in patients with head and neck squamous cell carcinoma. It can be used initially, which is known as neoadjuvant or induction therapy, or combined with radiotherapy, which is known as concomitant treatment and is currently considered the standard treatment for advanced neoplasms. And this is where the main controversy lies, in knowing what the usefulness and indications of induction and concomitant treatment are. In various forums, the discussion revolves around deciding whether a patient with advanced cancer should receive induction therapy, concomitant chemoradiotherapy or surgery as initial treatment and subsequently adjuvant therapy.

Based on current evidence, this editorial succinctly summarizes the indications for each one of these treatments.

When a squamous cell carcinoma is diagnosed at a locoregionally advanced stage in the head and neck area, systemic treatment is useful in two different scenarios: 1) as an attempt at organ preservation and 2) in locally advanced disease without the need or indication for preservation.

- Candidates for organ preservation, specifically of the larynx: patients whose only therapeutic alternative is voice mutilation (total laryngectomy) and non-surgically preserving the organ is attempted.
- With locoregionally advanced disease, whether resectable or not: the main goal is oncological control, and the secondary, organ function with low morbidity should surgical rescue be required.

Non-surgical larynx preservation is indicated in patients in whom the organ is functional, and should be avoided in those who require tracheostomy, or who have severe laryngeal dysfunction or extralaryngeal tumor extension. Preservation can be carried out in two forms: with concomitant chemoradiotherapy or with induction therapy followed by radiotherapy if the response is complete or by concomitant chemoradiotherapy if the response is partial. Although the standard of care continues to be concomitant chemoradiotherapy, induction therapy has three benefits^{2,3}:

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- 1) It selects patients who will have an excellent response to radiation therapy.
- 2) It identifies patients who have a poor prognosis and favors for them to early undergo laryngectomy, thus avoiding future complications associated with chemotherapy and radiation combined treatment.
- 3) It reduces the morbidity that usually occurs in case of rescue due to a failed concomitant treatment.

In turn, concomitant chemoradiotherapy, which is the standard treatment, implies that when there is not a proper selection we will not see the results but until the end of treatment, and in case of disease persistence, surgical rescue not only is much more complex, but also much more morbid, which markedly increases the rate of complications, such as the need for feeding tubes, pharyngoraphy dehiscence and flap necrosis, among others.

The cancer-unrelated mortality rate in patients with laryngeal cancer treated with concomitant chemoradiotherapy has been reported to have increased, and this is probably due to the treatment-associated complications the patient experiences, mainly bronchial aspiration at the time of swallowing. It has been estimated that 26.5% of patients receiving concomitant chemoradiotherapy have severe swallowing problems, and that 15% require gastrostomy tube, which is opposed to organ preservation principles, since, by definition, larynx-preservation treatment must preserve phonation, swallowing and ventilation functions⁴.

Although induction chemotherapy does not increase the rate of organ preservation or survival, it does allow selecting and differentiating patients who should receive the classic treatment (laryngectomy) from those who can continue with organ-preservation, either with radiotherapy alone or with concomitant chemoradiotherapy.

Patients who receive induction treatment with preservation intent may have partial or complete response, although, in both cases, it is accepted to continue the preservation attempt with radiotherapy, because the rate of post-radiotherapy persistence is higher in those with a response of less than 80%; in these cases, in the event of persistence, changing strategy and offering total laryngectomy is currently preferred³.

In those patients with advanced disease who do not require preservation, two groups can be distinguished:

A) Patients with primary tumor originating in an anatomical area of the head and neck whose initial treatment is usually surgery (oral cavity, larynx, hypopharynx and central facial skeleton). In turn, they can be divided in two subgroups:

A1) Surgically resectable.

A2) Unresectable or resectable but the magnitude of surgery implies great functional deficit or high morbidity (mainly severe-absolute dysphagia).

B) Patients whose primary tumor is not candidate for surgery (oropharynx). They can also be divided in two subgroups:

B1) Non-smokers or alcohol drinkers positive for human papillomavirus (HPV).

B2) Without human papillomavirus (HPV-negative) or alcohol and tobacco users.

In group A1, the best way to achieve locoregional control and perform appropriate staging is surgery, so that, according to the risk factors identified on histopathological analysis, adjuvant treatment can be decided.

In group A2, therapeutic alternatives are two: concomitant chemoradiotherapy, with the morbidity it implies, or induction chemotherapy with response evaluation after the first or second cycle. If the response is such that it allows surgery to be performed, the patient should undergo surgery and continue treatment with concomitant chemoradiotherapy or radiotherapy alone as adjuvant treatment; if the response does not allow a safe surgery, then treatment should continue with radiation therapy.

How to decide if we should offer induction for subsequent surgery? There are no rules for this, but this technique (induction for downstaging) will be preferred in those patients who theoretically can undergo surgery but sequelae preclude it (lingual tumors that go beyond the midline, oral tongue infiltration to the base of the tongue, bilateral tumors of the floor of the mouth with normal lingual function). Concomitant chemoradiotherapy will be indicated in those patients whose tumor volume and secondary dysfunction preclude surgery even after a complete response to induction, such as tumors that massively infiltrate the tongue, its intrinsic musculature, the base of the tongue, pre-cervical fascia, etc.⁵.

Subgroup B1 is considered of good prognosis, and although standard treatment is still the combination of chemotherapy and radiotherapy, as in B2 (HPV-negative), there is the possibility of reducing the radicality of treatment and thereby morbidity, which has been called "dose de-escalation". This is achieved with induction chemotherapy and, in case of complete response, continuing with radiotherapy, preferably with intensity-modulated technique, at a lower dose and with fields reduced to the area at highest risk. On the other hand, in those patients who fail to respond after chemotherapy or who experience tumor progression, treatment will be concomitant chemoradiotherapy.

Subgroup B2 (HPV-negative) has a poor prognosis, and although studies are analyzing the possibility of reducing radiotherapy doses according to the response to chemotherapy, the association of chemotherapy and radiation is considered standard.

The treatment of squamous cell carcinoma of the head and neck area is complex. It must be decided in a multidisciplinary manner and by consensus, and its main goal is to obtain the standard of control for each one of the stages and avoid offering unnecessary treatments or treatments that cause high toxicity and quality of life further deterioration.

The association of the three basic cancer treatments (surgery, chemotherapy and radiation) must be decided according to current scientific evidence.

Conflicts of interest

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