

Standard of care for locally advanced head and neck cancer (LA-HNSCC)

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Magnitude of the problem

HNSCC account for around 500,000 new cases per year. 2/3 of the patients present with advanced stages and most of them confess a long history of tobacco consumption and alcohol abuse. As a result we have to deal both with the cancer and the comorbid illness induced by this lifestyle.

LA-HNSCC require combined treatments that may generate notable cosmetic/functional sequels and that may hardly be undergone by patients with poor PS and impaired nutritional balance. The cure rate does not exceed 30%, the outcome is dominated by local and/or regional recurrences in >50% and distant metastases in at least 1/3 of the cases.

Advances in HNSCC management

Over the past three decades notable advances have been achieved.

Advances in surgery

With time, surgery [1] for LA-HNSCC has been less and less mutilating:

- Less extensive surgery: for example, the ‘mandibular swing’ as an alternative to hemimandiblectomy, the supracricoid laryngectomy as an alternative to total laryngectomy or the modified/selective neck dissections.
- More reliable reconstructive surgery. The myocutaneous flaps (in particular the major-pectoralis flap) allowed larger resections with reliable reconstructions and definitely reduced the morbidity of salvage surgery. More recently the free flaps have provided impressive cosmetic/functional rehabilitation after major head and neck surgery.

Advances in radiation therapy (RT)

In order to improve the loco-regional control after RT two major approaches have been explored:

- (1) hyperfractionated RT (to increase the total dose).
- (2) accelerated RT (to reduce the overall treatment time and cell repopulation). These two schedules provided better loco-regional control and survival but at the price of a higher acute and late toxicity [2].

Apart from these altered fractionations, the use of radiosensitisers improved the radio-biologic effects while new techniques (conformal RT, intensity modulated RT) have improved the delineation of the volume to be irradiated.

Advances in chemotherapy

The appearance in the early 1980s of platinum-based regimens (in particular, the association of cisplatin and 5-fluorouracil), providing impressive response rates, have opened a new era in the management of LA-HNSCC.

A large meta-analysis [3,4] has assessed the survival benefit adding chemotherapy in protocols with curative intent. Adjuvant chemotherapy or induction chemotherapy (ICT) as a whole did not provide any benefit. But when ICT consisted of cisplatin-5FU, a significant 5% benefit in survival was observed. The greatest benefit was obtained with concurrent chemoradiation (CRT): 8% up to 11% for RT combined with cisplatin alone.

The correlation between chemosensitivity and radiosensitivity was the rationale for the first generation of organ (larynx) preservation clinical research. Patients treated by ICT followed by RT in good responders had a survival and ultimate disease control similar to those treated by total laryngectomy and the larynx could be preserved in nearly 60% of the cases. The second generation of larynx preservation trials integrated CRT that provided a higher larynx preservation rate (more than 80%) than ICT but with a higher acute and late toxicity and without any advantage in survival [5].

Patients treated by surgery with positive margins and/or extracapsular spread are likely to recur and/or

to develop distant metastases. Randomised trials comparing postoperative RT alone or combined with chemotherapy have definitely concluded in a better outcome after CRT [6].

More recently, molecular targeted therapy (MTT) has gained interest in head and neck oncology. Due to the overexpression of the EGF receptor in more than 90% of head and neck squamous cell carcinoma and the correlation between this overexpression and a poor outcome, clinical research has been conducted targeting this pathway. To date, only one randomised trial RT with a monoclonal antibody (cetuximab or Erbitux®) has been published. Both locoregional control and overall survival were significantly improved without an increased radiotherapy-induced mucositis but with a skin toxicity [7].

In parallel, there are converging data from randomised trials [8–10] on the superiority of ICT with docetaxel (Taxotere®) added to cisplatin-5FU over cisplatin-5FU alone in terms of locoregional control and survival. These data have undoubtedly reopened the discussion on ICT that lost interest when data on CRT had been published.

Finally, new approaches with ICT followed by CRT and integrating MTT are under evaluation.

Where do we go from here?

All these advances must be considered in perspective with the important and permanent improvements in tumour definition mixing imaging features and biological parameters. More than ever a multidisciplinary discussion (head and neck surgeon, radiation therapist, medical oncologist, radiologist, internist, biologist) is mandatory to better design basic and clinical research programmes and to fine-tune decision making for the selection of the most appropriate treatment for each patient.

At the moment, in the daily practice, the standard of care for LA-HNSCC consists of:

- *A thorough work-up including:*
 - Clinical examination and endoscopy under GA with biopsy;
 - General (physical, psychological, social etc.) evaluation and nutritional balance control;
 - Complete imaging evaluation (CT scan, MRI, and PET scan according to each situation);
 - Dental status evaluation and care.
- *A multidisciplinary discussion for decision making:*
 - Inclusion in an on-going trial or

- Proposition of a validated therapeutic option, i.e. at the moment:
 - Surgery with postoperative CT (\pm concurrent chemotherapy)
 - Definitive RT (with or without altered fractionation)
 - ICT and RT CRT and medical treatment (cytotoxic drugs or MTT)
 - Organ preservation if indicated.
- *A thorough follow up looking for:*
 - Local and/or regional and/or distant failure;
 - Second primary tumour;
 - Treatment side effects;
 - Comorbid illness;
 - Pain and/or denutrition
 - Need for functional rehabilitation and/or social reinsertion.

Conclusions

LA-HNSCC require heavy and combined therapies that are sometimes compromised in patients presenting with notable comorbidities. Supportive care also plays an important role in conjunction with anti-tumour strategies. The impressive advances in surgery, radiotherapy and medical treatment have tremendously broadened the therapeutic armamentarium. In parallel, advances in imaging and biology have allowed a better identification of these tumours and of their hosts. All these advances must be taken into account for decision making. This comprehensive approach definitely requires a multidisciplinary collaboration that is today the only one golden standard of care.

Conflict of interest statement

The author is a member of the Advisory Boards of both Sanofi-Aventis and Merck KGaA.

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