

# STATE OF THE ART IN THE MANAGEMENT OF ADVANCED HEAD AND NECK CANCER

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## ABSTRACT •

**U**PPER AERODIGESTIVE tract cancer usually presents as advanced disease with a dismal prognosis. Chemotherapy has been used in order to enhance local control and treat any systemic disease but results have been modest. Recently, chemotherapy administered simultaneously with radiotherapy has showed to be superior to radiotherapy alone in treatment of unresectable tumors. This approach has been used as a promising alternative in the treatment of resectable tumors in order to obtain organ conservation. Nevertheless these treatments are toxic and expensive limiting its ample use. Investigation has been focused in identify more active and less toxic schedules. Biological therapies offer one interesting alternative.

**Key words:** Head and Neck Cancer, Treatment, Chemo-radiation.

## RESUMEN •

**E**L CÁNCER de las vías aerodigestivas superiores comúnmente se presenta como enfermedad avanzada con un mal pronóstico. La quimioterapia se ha ensayado con el objeto de mejorar el control local y tratar la eventual enfermedad sistémica, pero los resultados han sido modestos. Recientemente, la quimioterapia concomitante con radioterapia ha demostrado ser superior a la radioterapia sola en el tratamiento de los tumores irresecables y una prometedora alternativa en el manejo de los tumores resecables cuando se desea conservar órganos. Sin embargo estos tratamientos son tóxicos y costosos lo que ha limitado su amplio uso. La investigación se dirige a identificar esquemas más activos y menos tóxicos. La terapia biológica ofrece interesantes expectativas.

**Palabras Clave:** Cáncer de Cabeza y Cuello, Tratamiento, Quimioterapia.

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## INTRODUCCIÓN •

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In México, over 3,000 new cases of head and neck cancer are diagnosed every year and more than 1,800 patients die due this cause (1). Upper aero digestive tract cancer represents 3% of all malignant neoplasms and most of them affect larynx (1.0%) and oral cavity (0.8%). Unfortunately more than 65% are diagnosed in advanced stage, associated with dismal prognoses: 5-year survival is 10 to 40% according specific site and resectability; meanwhile lethality is 60% (1). In the European Union, more than 72,000 new cases are diagnosed every year and cause 31,000 deaths. In the USA more than 45,000 cases are diagnosed per year, representing 3-4% of all cancers (2) and more than 11,000 patients die per year. Worldwide more than 500,000 new cases are diagnosed every year.

It is well known that tobacco and alcohol consumption explains 90% of the cases and that squamous cell carcinoma (HNSCC) is the major histological diagnosis, and accounts more than 90% of all carcinomas.

Patients in early stages of disease are treated with radiation or surgery as a single modality with similar oncologic results; i.e. results usually are good, more than 80% survive at 5 years; meanwhile the management of patients with advanced HNSCC represents a complex decision, because prognosis is dismal (10-50% 5-year survival) but functional and esthetic results usually are unsatisfactory. In order to optimize results of treatment, patients with locally advanced disease should be evaluated and treated by multidisciplinary team, constituted by surgeons, radio-oncologist, medical oncologist and specialists in rehabilitation.

In locally advanced resectable disease standard treatment is a combination of surgery and radiation therapy, but in unresectable tumors and some patients who deny surgery or does not are surgical candidates, treatment usually consists in concomitant chemoradiation (3).

In addition, patients now consider more important maintaining quality of life than prolonging life and it has been assumed that organ conservation is an im-

portant issue in maintaining quality of life; due this, investigations has been directed toward this objective. Selective neck dissections, partial laryngeal surgery, bucofaringeal and faringo-laryngeal laser surgery, marginal mandibulectomy, orbital conservation surgery and radio-guided surgery are examples of efforts directed toward organ conservation. Another approach is using chemoradiation in order to avoid surgery. Published data, specifically a meta-analysis showed a discrete but significant increase of survival between patients with advanced disease treated with neoadjuvant chemotherapy (4) vs surgery and radiotherapy, although these results must be balanced against higher toxicity. More recently, simultaneous radio-chemotherapy has demonstrated to be superior to radiotherapy alone in terms of local control and survival in patients with advanced unresectable tumors. This observation conduced to the hypothesis that simultaneous chemoradiation would be an alternative for organ conservation in advanced resectable tumours (5).

It has been claimed that chemoradiation is superior in resectable tumours but the comparison with radiotherapy and salvage surgery in resectable tumours is inappropriate. Standard treatment for resectable tumours, against chemoradiation must be compared is a planned schedule of surgery and postoperative radiotherapy (6). Similarly, other studies stated that better results were observed in resectable tumours but, again, it is a misconception because they must compare a planned schedule of surgery and postoperative radiotherapy and not with radiotherapy alone (7, 8). Consequently, these studies should not be accepted as evidence that chemoradiation is superior in advanced resectable tumours respect to surgery plus radiotherapy in terms of local control or survival, but they do not reject the hypothesis that chemoradiation would be a valuable approach for organ conservation. Indeed, now there is some strong evidence. Forastieri showed that concurrent chemoradiation is superior in terms of laryngectomy-free survival to sequential chemoradiation (neoadjuvant chemotherapy and radiation) and even better than radia-

tion alone in advanced but resectable laryngeal cancer. Remarkable, this trial did not include T3, N0, M0 glottic tumors nor voluminous tumors or with advanced cartilage involvement (9).

Other approaches in order to obtain organ conservation are based on new radiation schedules. A group of the University of Wisconsin has described a technique with a linear accelerator-based radiation therapy in which radiation beams are modulated (IMRT) producing a highly conformal dose distribution (1). The primary objective of IMRT is to reduce the dose in surrounding normal tissues in order to reduce toxicity and preserve function, meanwhile maintaining full-dose delivery to tumor. Hiperfractionated radiotherapy, accelerated radiotherapy and radiotherapy with concomitant boost are other valuable and promising approaches.

### **WHAT IS THE BEST SYSTEMIC TREATMENT IN 2007 FOR HEAD AND NECK CANCER? •**

In the past 25 years, an impressive number of publications evaluating thousands of patients with a number of different therapeutic modalities has been published (11), adjuvant, induction, neoadjuvant and concomitant chemotherapy with radiation are some modalities used in different circumstances too: for locally advanced resectable, for unresectable and finally for metastatic disease. These trials test a number of antineoplastic agents administered as a single agent or scheduled combinations. Recently, Forastieri reviewed this issue (12).

### **PALLIATIVE CHEMOTHERAPY •**

Palliative chemotherapy is justified when a patient with a no-curable disease suffers manifestations like pain, bleeding or mal odour. In this situation chemotherapy would alleviate these symptoms, but a transitory response must be balanced against toxicity.

Since many years, combination of platin plus 5-fluorouracil (cisplatin 100 mg/m<sup>2</sup>, day 1, and 5-fluorouracil 1,000 mg/m<sup>2</sup> in 24 hr continuous IV infusion on day 1 through 4 every 3 weeks) has been the standard treatment for unresectable disease usually

followed by radiotherapy. Recently, it has been tested with subsequent chemoradiation, and occasionally, in very selected patients, by radical surgery. Overall results in terms of response are around 27% (CR and PR). In addition, other combinations are associated with similar results. In a recent publication, ECOG compared this combination versus paclitaxel and cisplatin, but final results showed there is not any difference in survival between both groups (13).

### **POSTOPERATIVE/ADJUVANT CHEMOTHERAPY •**

The use of postoperative or adjuvant chemotherapy in high-risk patients remains under evaluation. A study analyzed 442 evaluable patients and didn't show any difference in overall survival (4-year actuarial survival rate was 44% on the RT arm and 48% on the CT/RT arm [p = n. s.]), 4-year disease-free survival (38% vs. 46%, p= n.s), nor 4-year local-regional control rates (29% vs. 26%, p= n.s). However, the overall incidence of distant metastases was 23% on the RT arm compared with 15% on the CT/RT arm (p = 0.03). This trial confirmed the activity noted in previous trials employing neoadjuvant chemotherapy, but without improvement on overall survival (14).

Recently and independently, Cooper and Bernier published their own results with other approach. They used postoperative concomitant chemoradiation in randomized controlled trials with high-risk patients because positive margins, extracapsular spread, perineural invasion, and lymphatic and vascular involvement. They found a significant difference in relapse free survival, but one of them also showed a significant difference in overall survival (32, 33). They concluded that postoperative chemoradiation is a valuable tool treating patients with a high risk of relapse. But administration must be balanced against high toxicity in a group with debilitated patients.

### **INDUCTION CHEMOTHERAPY •**

By definition, induction chemotherapy is used in advanced unresectable patients in order to obtain a major response that eventually permits subsequent resection and better prognosis. Neverthe-

less trials are confusing because they usually use induction chemotherapy as synonymous of neoadjuvant chemotherapy for resectable patients.

Initial studies comparing induction chemotherapy versus radiotherapy alone, reported that the overall survival was not improved by the addition of induction chemotherapy (23% vs 16% in 5-year survival and in 10-year survival was 19% vs 9%;  $p = n.s$ ). Another study used preoperative chemotherapy versus local therapy alone, this trial showed no significant difference in survival (5-year survival: 31% vs 43%, and 10-year survival 23% vs 14% ( $p = ns$ .) but among inoperable patients those received induction chemotherapy had much better survival (5-year survival; 21% vs 8%; and 10-year survival; 16% vs 6%). There were also some differences in relation with the presence of distant metastasis and local failures, specifically; there was a significant reduction in the group receiving induction chemotherapy. (15)

Induction chemotherapy followed by chemoradiotherapy in head and neck cancer patients with locally advanced disease, should be considered. Some phase II single-institution studies are ongoing in order to demonstrate whether this approach reduces possibilities of developing metastatic disease or local recurrent disease (16).

## **NEOADJUVANT CHEMOTHERAPY •**

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By definition neoadjuvant is used in advanced resectable disease in order to enhance results. In a trial by El-Sayed and Nelson (19) 5-FU and cisplatin was used as neoadjuvant therapy prior to surgery. They demonstrated a very high rate of clinical response, ranging from 57% to 80% which may be associated with high percentage of pathologic complete responses.

Three meta-analyses reviewed by Licitra and Vermorken concluded that neoadjuvant chemotherapy was associated with a statistically significant advantage in survival, but this figure was low: 4% at 2 to 5 years (17). But these metaanalysis also showed that improvement in survival was mainly based on the most robust improvement obtained with the concomitant use of chemotherapy and radiotherapy

(7% absolute benefit at 2 years and 8% at 5 years). On the other hand neoadjuvant chemotherapy did not have any significant advantage in the meta-analyses performed by Pignon (14).

In conclusion, the evidence suggests that there is a small but statistically significant benefit on survival when neoadjuvant chemotherapy is added to a locoregional treatment in patients with non-metastatic and resectable head and neck cancer, but most of the investigators think that neither adjuvant chemotherapy nor neoadjuvant chemotherapy provided significant benefit; therefore these modalities should not be used outside clinical trials.

In other context, a review of ten randomized trials including 2,450 patients receiving neoadjuvant, concurrent and/or adjuvant chemotherapy to radiation in the treatment of locally advanced nasopharyngeal carcinoma showed that addition of chemotherapy produced absolute survival benefit of 4% after 5 years. Three categories were defined according to the sequence of chemotherapy: neoadjuvant chemotherapy, addition of concomitant chemoradiotherapy and adjuvant chemotherapy. The best results were seen in the group of patients that received concomitant chemoradiotherapy, with a survival advantage of 20% in 5 years. This study concluded that addition of chemotherapy to radiotherapy is the most effective approach (20).

## **CHEMORADIOTHERAPY •**

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De la Garza et al, in 1975 were the first in Mexico to use simultaneous chemoradiotherapy in locally advanced head and neck cancer; they used concomitant bleomycin and radiation (21). Results showed a significant initial benefit, in comparison with patients receiving radiotherapy alone, however radiotherapist and surgeons were not interested in participating in another similar studies. Since then this author think this modality is a better option for the treatment of patients with locally advanced head and neck cancer (13).

Since 20 years ago it has been published a number of trials combining several cytotoxic drugs and recently,

monoclonal antibodies with different radiation regimens. These trials show an improved outcome in patients with locally advanced head and neck carcinoma.

At the M.D Anderson Hospital four different trials using radiotherapy with standard fractionation, with or without high-dose cisplatin as a single agent every 3 weeks in treatment of locally advanced non-nasopharyngeal cancer have been reported in the past two years. All four trials showed that the combined regimen with chemotherapy were superior than radiation alone in terms of local control and/or organ preservation; in addition, two trials showed better overall survival. Major toxicity was mucositis, which was reported as very severe (100 mg/m<sup>2</sup> cisplatin/3 weeks), requiring intensive premedication and supportive care (22); the French Head and Neck Oncology and Radiotherapy Group (GORTEC) reported similar results. They revealed that morbidity of the combination of radiation concurrent with carboplatin and fluorouracil was significantly higher than radiation alone.

On December 2004, a trial (23) showed an improved outcome of patients with locally advanced HNC by rational modification of radiation fractionation regimens or combinations of radiation with chemotherapy. This item has been object of intensive investigation for more than three decades. In addition, two ongoing cooperative trials have been designed; RTOG trial compares the efficacy of an accelerated fractionation regimen (concomitant boost: 72 Gy in 6 weeks) plus cisplatin to standard fractionation (70 Gy in 7 weeks) plus cisplatin. The three-arm GORTEC study compares accelerated fractionation schedule (70 Gy in 6 weeks) plus carboplatin-fluorouracil to a more pronounced accelerated fractionation (64.8 Gy in 3.6 weeks) without chemotherapy and the standard fractionation schedule plus carboplatin-fluorouracil. Both trials are approaching completion of accrual and results will be reported in 2 to 3 years.

Remarkably, concomitant chemoradiotherapy is associated with higher toxicity that limits its wide use. Severe mucositis may occur in more than 70% of patients treated with radio chemotherapy and

xerostomy is a significant long-term sequel.

Amifostin is an aminothioliol prodrug that protects mucosal tissue from chemotherapy and radiotherapy induced damage. Recently a trial phase III trial reported a significant reduction of intensity of xerostomy after two year since conclusion of treatment on those patients treated with Amifostin before radiotherapy or radio-chemotherapy. Locoregional control rate, progression-free survival, and overall survival were not different between the amifostine group and the control group. (24).

In nasopharyngeal cancer, Huguenin et al (25) using cisplatin (two cycles 20 mg/m<sup>2</sup> on week days 1 to 5) and hyperfractionated radiotherapy, in advanced disease, concluded that the therapeutic index of hyperfractionated radiotherapy was improved by concomitant use of cisplatin. Langendijk et al (26) published a meta-analysis of ten randomized clinical trials in order to determine the value of additional neoadjuvant, concurrent and/or adjuvant chemotherapy and radiation in the treatment of 2,450 patients with locally advanced nasopharyngeal carcinoma, they concluded that the results indicated that concomitant chemotherapy in addition to radiation is the most effective way to improve the overall survival in nasopharyngeal carcinoma.

Recently, Vermorken et al (27) used cetuximab, an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR) (400 mg/m<sup>2</sup> initially and 250 mg/m<sup>2</sup> / week) as a single treatment and cetuximab plus platin, in 330 patients who failed to first line treatment with platin. He observed that median survival time of 6 months achieved with cetuximab in platin-refractory is similar to that seen with first-line therapy and represent an increase in survival of 2.5 months compared with platin-refractory historical controls. They concluded that cetuximab monotherapy seems to be a good option in patients with recurrent or metastatic disease.

In addition, Baselga et al (28) published a multicentric study with 96 patients with HNSCC platin

refractory, using cetuximab in combination with platin-based chemotherapy; purpose of this study was to evaluate efficacy and safety. They observed a disease control disease of 53% (PR or stable disease) with a median time to progression and overall survival of 85 and 183 days. Investigators concluded that combination of cetuximab and platin is a valuable tool in the treatment in these poor-prognosis patients with platin refractory recurrent or metastatic HNSCC.

Recently Aguilar et al published an experience with 27 valuable patients with advanced unresectable disease. Treatment consisted in weekly gemcitabine concurrent with radiotherapy (29). Using two different low doses, 50 mg/m<sup>2</sup> and 100 mg/m<sup>2</sup>, overall complete response was 61%, partial response was 27% with a global response of 88% and the median duration of the response of 21 months. Mucositis grade 3-4 was 74% and was the main limiting toxicity, but manageable in the most of the cases. Finally, 25 patients (93%) received at least 80% of the prescribed total dose of radiotherapy.

More recently, from march, 2004 to September 2005, Aguilar et al studied 28 patients with local and regionally advanced and unresectable HNC using a combination of concomitant chemoradiotherapy alternating weekly schedule using gemcitabine and cisplatin concomitant with radiotherapy, each week with doses of 100 mg/m<sup>2</sup> and 50 mg/m<sup>2</sup> respectively. The median age, in eleven patients was in a range of 35-59 years and seventeen patients were in the range of 60 or more years. The rationale of this study was to probe if combination of two synergistic and radiosensitizers drugs could produce better results in term of complete response with less oral toxicity. Preliminary results (in press) showed a better complete response than previous study. Twenty-one out of 28 patients, 21 (75 %) reached complete clinical response, and 5 (17%) a partial response for an overall response of 92%.

Oral toxicity grade 3-4 was observed in 42%.

The same author is using a schedule of gemcitabine plus cetuximab concurrent with radiotherapy. Cetuximab is used as previously reported: 400 mg/m<sup>2</sup> of induction previously to radiotherapy, followed of 250 mg/m<sup>2</sup> weekly. Authors plan to evaluate 41 patients with locally advanced disease. At present 20 patients have been treated (T1, N2, M0; T2, N2, M0; T3, N0-1, M0; T4, N0-3, M0). Preliminary results show a remarkably high response without higher toxicity.

## CONCLUSION •

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Much awaits to be learned about the best treatment for patients with HNSCC. But concomitant chemoradiotherapy seems to be the standard of care for patients with advanced unresectable HNC and for organ conservations trials.

In stages III and IV, patients with locally advanced disease the use of 5-FU infusion, concomitant with radiotherapy has been the “standard”, however others agents with concomitant radiotherapy have demonstrated better responses and disease free survival. Other drugs as taxanes are waiting for further evaluation. More recently, monoclonal antibodies seem to offer better responses with a more favorably toxicity profile.

Remarkably, the most significant prognostic factors for poor outcome are extracapsular spread from neck nodes and microscopically involved resection margins, these parameters define a group especially amenable for trials testing adjuvant treatment (29).

In selected patients with metastatic disease, systemic chemotherapy and or radiotherapy can offer symptomatic benefit, but overall responses and disease free-disease are low, however the new agents would provide a valuable tool for metastatic and platin refractory tumors in terms of quality of life.

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