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Late toxicity after radical treatment for locally advanced head and neck cancer

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SUMMARY

Background: Multimodal treatment for locally advanced head and neck carcinomas (LAHNC) has been reported to improve survival. However, it is less clear to what extent this survival gain is given at the expense of an impact on the quality of life of our patients. Our aim is to analyze the ongoing late toxic effects among long survivors, to determine how much these impairments affect their QoL, and if there is any factor that clearly impacts on this toxicity.

Methods: 152 Patients diagnosed with LAHNC were treated radically in our clinical practice, either with concomitant chemoradiotherapy or bioradiotherapy, with or without induction chemotherapy. We prospectively assessed these patients' treatment-related late toxicities according to the Radiation Therapy Oncology Group scoring system, and patients answered a QoL question to subjectively evaluate the degree of impact caused by these sequelae in their daily life. Multivariate logistic regressions were performed to detect factors that could influence in toxicity.

Results: 21.9% Patients experienced grade 3–4 toxicity. Concomitant chemoradiation with cisplatin was found to be a risk factor of moderate and severe late toxicity compared to concomitant cetuximab in the adjusted analysis by RT fractionation. OR for moderate toxicity 0.292 (CI: 0.125–0.680, $p = 0.004$); OR for severe toxicity: 0.299 (CI: 0.0909–0.999, $p = 0.05$). Induction chemotherapy was found to be a protective factor for moderate late toxicity compared to concomitant treatment alone.

Conclusion: Patients treated with concomitant chemoradiation with cisplatin have significantly more late toxicity compared to bioradiotherapy, whereas induction chemotherapy prevents from developing moderate late toxicity.

Introduction

Head and neck cancers are a heterogeneous group of cancers that arise from the squamous epithelium in the cavities of the head and neck area. Statistics of patients with squamous cell carcinoma of the head and neck indicate a gradual trend to increased survival of these patients. A recent review about changes in survival in the late 20th and early 21st century demonstrated a major statistically significant improvement in survival among head and neck cancer patients. The overall 5-year relative survival rate went from 54.7%

Abbreviations: LAHNC, locally advanced head and neck carcinomas; CRT, chemoradiotherapy; BRT, bioradiotherapy; RT, radiotherapy; RTOG, radiation therapy oncology group; QoL, quality of life question; HPV, Human Papiloma Virus; IMRT, Intensity-Modulated Radiation Therapy; EORTC, European Organization for Research and Treatment of Cancer; CCRT, concomitant chemoradiotherapy treatment; PF, Cisplatin–5Fluorouracil; TPF, Docetaxel–Cisplatin–5Fluorouracil; PPF, Paclitaxel–Cisplatin–5Fluorouracil.

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in 1992–1996 to 65.9% in 2002–2006. Notably, improvements in cancer of the oral cavity, tongue, tonsils and nasopharynx were observed in the subgroup analysis, with the greatest improvements observed in tonsillar carcinoma and carcinoma of the tongue [1].

Therapy for head and neck cancer has evolved over the past decade. Significant efforts have been made to improve multimodal treatments, adding new therapeutic options for these patients, which have translated into better survival results. Several studies have hypothesized that certain factors might have been responsible for these positive results: the Human Papiloma Virus (HPV) appearance in certain oropharynx sublocalizations [2], improvements of surgical techniques with the emergence of robotic surgery and microvascular flaps, the emergence of new radiotherapy techniques such as the implementation of the Intensity-Modulated Radiation Therapy (IMRT) [3] the use of combined chemotherapy (cisplatin) [4] or biotherapy (cetuximab) [5] regimens alongside with radiotherapy or more intensive induction chemotherapy schedules (Do cetaxel–Cisplatin–5Fluorouracil) [6].

However, these encouraging results are accompanied by a not unworthy toxicity. We cannot assure whether the mortality is closely associated with patient's comorbidity: either the mortality is increasing by using a more aggressive approach, or it is declining due to learning curve completion of these new therapies and the accurate implementation of supportive care measures. Taking into consideration that our long survivors may develop chronic toxicities related to our treatments, we need to assume that these limitations will certainly have an impact on their daily activities for the rest of their lives. Hence, it is time to better characterize and quantify this chronic toxicity and to start developing effective rehabilitation programs, in order to restore the functionality of our patients as much as we can. It is well known that patients heal physically after treatment, but as clinicians we must be able to improve its undesired consequences and to reduce the impact that an impaired capacity may have in our patients' social relationships.

Remarkably, there are important variations in the toxicity reporting methods, which has lead to a certain confusion in the past, and this is even more pronounced when it refers to evaluating long-term toxicity [7–9]. Unfortunately, there is a lack of information, since the vast majority of clinical trials published to date do not report long-term outcomes regarding late toxicity. The aim of this study is to analyze the late toxic effects present among our LAHNC long survivors and to determine how much these chronic toxicities may affect their lives. We will also pursue to explore whether any clinical or epidemiological factors could be related with the severity of the toxicity. The knowledge of these factors could translate into better tailored treatment strategies, towards a more personalized medicine for our LAHNC patients.

Material and methods

To develop this study at our institution, we prospectively assessed 152 LAHNC long survivors treated radically between March 1994 and July 2010. All of them had received either concomitant treatment with CRT or BRT, or fractionated RT with or without induction chemotherapy. The late toxicity assessment coincided with planned follow-up appointments in the Head and Neck Oncology Unit, so no additional appointments were needed. If the eligible patients were keen to participate into the study, they completed the proposed assessments that same day. Patients graded their treatment-related late toxicities according to the RTOG scoring system, and answered a QoL question to subjectively evaluate the degree of impact caused by these sequelae in their daily life.

A prospective analysis was conducted among all long-term survivors, treated for a stage III/IVa-b LAHNC at the Head and Neck Oncology Unit at our Institution. We considered as a long-term survivor that patient who lived more than two years since the diagnosis with no diagnosis of recurrence disease. The median time between treatment completion and evaluation was 60 months (24–214).

Patients and treatment

We selected 152 consecutive patients followed as an outpatients, that underwent radical treatment between January 1994 and January 2010. All cases were initially discussed by our multidisciplinary head-and-neck oncology team for tumor staging and treatment recommendations. Routine pre-treatment evaluation consisted of a complete medical history, physical examination, endoscopic evaluation, blood test, computed tomography (CT) or magnetic resonance imaging (MRI) and chest X-ray or chest CT. State of mind of patients and their social situation were also explored.

All patients had a LAHNC from the oral cavity, larynx, hipopharynx, oropharynx, nasopharynx or unknown primary from the head and neck area. We excluded patients previously treated with surgery, those who were treated with palliative intent or if they had less than 24 months of follow-up. All patients had received treatment with radical intention. During the treatment, patients were seen almost once a week by a radiation oncologist, a medical oncologist, a specialist nurse, an oral surgeon, an ENT surgeon and a dietician and even more frequently when necessary. Acute adverse effects, oral intake, weight, vital signs and concomitant treatments were thoroughly documented. After completion of treatment, patients started their follow-up visits performed by the treating physicians. Each visit consisted of a history of medical symptoms, physical examination, endoscopic evaluation when needed, and toxicity assessment. Radiologic evaluation was done once a year for the first three years or when a relapse was suspected. Follow-up data were reviewed from January 2012 to January 2013 in the follow-up visits with each patient. All relevant examinations were performed, and patients also answered about changes in their QoL.

Late morbidity assessments

We prospectively reviewed consecutive long-term survivors in an outpatient clinic, answering a subjective assessment of late toxicity based on the RTOG/European Organization for Research and Treatment of Cancer (EORTC) scoring system on skin, subcutaneous tissue, mucous membrane, salivary glands, larynx and bone (jaw). A prospective database was created containing one item for each kind of toxicity. We analyzed late toxicities in patients alive with more than 2 years of follow-up, and later on, these toxicities' correlation with the oxic habits of the patients, their tumor characteristics and previous therapies received. Toxic habits such as tobacco and alcohol abuse were recorded in different time points: before the diagnosis of the tumor, during the treatment and after completing the treatment.

A self-reported QoL question was completed by each patient; assessing how the side effects related to previous treatments affected their lifestyle. The answer was graded in several categories "normal live without limitations, partial restricted normal life, limited normal life and extremely limited normal life", to allow us to quantify the degree of limitation that the impairment caused them.

Statistical analysis

Frequency tables for each toxicity were performed. The presence/absence of moderate and severe toxicity was calculated adding the information of each toxicity item. Univariate and