Radiotherapy and Oncology 110 (2014) 422–428

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Quality of life in head and neck cancer

The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: A prospective cohort study

Irma M. Verdonck-de Leeuw [a,*], Laurien M. Buffart [b], Martijn W. Heymans [b], Derek H. Rietveld [c], Patricia Doornaert [c], Remco de Bree [a], Jan Buter [d], Neil K. Aaronson [e], Ben J. Slotman [c], C. René Leemans [a], Johannes A. Langendijk [f]

[a] Department of Otolaryngology/Head and Neck Surgery; [b] EMGO Institute for Health and Care Research, Department of Epidemiology & Biostatistics; [c] Department of Radiation Oncology; [d] Department of Medical Oncology, VU University Medical Center; [e] Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam; and [f] Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 5 November 2012
Received in revised form 3 January 2014
Accepted 12 January 2014
Available online 25 February 2014

Keywords:
Radiotherapy
Chemoradiation
Head and neck cancer
Quality of life
Survival

ABSTRACT

Background and purpose: To evaluate the course of health-related quality of life (HRQOL) from diagnosis to 2 years follow-up in patients with head and neck cancer (HNSCC) treated with chemoradiation (CRT).
Materials and methods: 164 patients completed the EORTC QLQ-C30 and QLQ-H&N35 questionnaires 1 week before and 6 weeks and 6, 12, 18, and 24 months after CRT. Patients were compared to a reference group. A linear mixed-model analysis was used to assess changes in HRQOL over time, and whether this was associated with age, gender, comorbidity, and tumor sublocation.
Results: Significant differences for the majority of HRQOL scales were observed between patient and reference group at baseline, and follow-up. The course of HRQOL was different for survivors compared to non-survivors. In survivors, improvement over time was observed (in global quality of life, physical, role, and social function, fatigue, pain, swallowing, speech, social eating, and social contacts), while in non-survivors the pattern over time was either no changes in HRQOL or a deterioration (in physical function, social eating and contacts). In both survivors and non-survivors, emotional functioning improved after treatment, but deteriorated in the longer term. Patients with comorbidity reported worse physical function, and patients with oral/oropharyngeal cancer (compared to hypopharyngeal/laryngeal cancer) reported more oral pain and sexual problems, but fewer speech problems.
Conclusions: The course of HRQOL of HNSCC patients during the first 2 years after CRT is different for survivors compared to non-survivors and is associated with comorbidity and tumor subsite.
 Radiotherapy and Oncology 110 (2014) 422–428

Head and neck squamous cell cancer (HNSCC) and its treatment may affect general domains of health-related quality of life (HRQOL), such as physical and emotional functioning, as well as HNSCC-specific HRQOL domains, such as oral health, speech, and swallowing [1]. Many patients with locally advanced cancer of the oral cavity, oropharynx, hypopharynx, and larynx are treated with radiotherapy and chemotherapy (chemoradiation (CRT)) or cetuximab. CRT is currently considered standard of care in patients with irresectable tumors. The advantage of CRT over surgery as primary treatment in patients with resectable tumors is the possibility of maintaining the normal anatomy of the larynx and oropharynx which are essential for speech and swallowing [2–7].

A limited number of prospective studies have investigated the impact of CRT on HRQOL in HNSCC patients treated with curative intent [8–13]. In all these studies, the course of HRQOL was investigated from pretreatment up to 6 months or 1 year after treatment. In general, these studies reported deterioration of HRQOL during treatment with gradual improvement during the first year after treatment [12,13]. Additionally, in 71 survivors with 5 year follow-up, no significant differences in HRQOL were observed compared to the 1 year follow-up assessment, except for xerostomia which improved in the long term. The 1 year HRQOL (fatigue, voice and swallowing) of the 71 survivors was significantly better than that of patients who subsequently died [13]. It is difficult to draw firm conclusions from previous studies about HRQOL of HNSCC patients after CRT due to methodological shortcomings, including a short follow-up, typically limited to the first year after treatment, high dropout rates and low study compliance, and the lack of HRQOL reference values from the general population.

* Corresponding author. Address: Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, PO BOX 7057, 1007 MB, Amsterdam, The Netherlands.
E-mail address: im.verdonck@vumc.nl (I.M. Verdonck-de Leeuw).

http://dx.doi.org/10.1016/j.radonc.2014.01.002
0167-8140/

The purpose of the present study is to evaluate (i) prospectively the course of HRQOL of a cohort of patients treated with CRT for advanced HNSCC from baseline up to 2 years after completion of treatment, (ii) to compare the patients' HRQOL with that of a reference group of healthy individuals, and (iii) to investigate if the course of HRQOL is associated with age, gender, comorbidity, and tumor location.

Materials and methods

Patients

The study sample consisted of 242 patients with advanced HNSCC treated between January 2000 and January 2008 in the VU University Medical Center in Amsterdam. Eligible patients were those diagnosed with primary squamous cell carcinoma of the mucosal surfaces of the oral cavity, oropharynx, hypopharynx, or larynx, and treated with curative chemoradiotherapy. Exclusion criteria were distant metastases, previous surgery or radiotherapy for HNSCC, brachytherapy, serious cognitive impairment or lack of basic knowledge of the Dutch language (68 patients). Ten patients declined to participate, resulting in a study cohort of 164 patients.

Sociodemographic (age, gender) and clinical variables (tumor subsite and comorbidity) were assessed by medical records audit. Comorbidity was classified according to the Adult Comorbidity Evaluation 27 (ACE-27) [14] and included cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, and immunological disorders, previously malignancy, severe weight loss or excessive alcohol intake. The ACE-27 has been designed specifically for cancer patients and classifies patients into 4 grades of comorbidity (none, mild, moderate, severe).

Treatment

Patients included in this analysis were treated with curative intent with CRT. Through 2003, patients in VU University Medical Center were treated with 3D-CRT, while since 2004 Intensity-Modulated Radiotherapy (IMRT) has been used. Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). In all patients, a contrast-enhanced planning CT scan was made in supine position using a thermoplastic mask. Patients treated with 3D-CRT received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumor and pathological lymph nodes to a total dose of 70 Gy, all in fractions of 2 Gy. No attempt was made to spare the salivary glands. In patients treated with IMRT, attempts were made to spare the parotid glands without compromising the dose to the target volumes by minimizing the mean dose to the parotid glands as much as possible. In general, a seven-field equidistant, non-opposing beam configuration was applied. Patients treated with IMRT were treated with a simultaneous integrated boost technique with bilateral elective irradiation of the neck nodes to a total dose of 57.75 Gy, using a dose per fraction of 1.65 Gy. The primary tumor and pathological lymph nodes were treated to a total dose of 70 Gy, in fractions of 2 Gy. Chemotherapy was given concurrently with radiotherapy and consisted generally of cisplatin 100 mg/m^2 intravenously on days 1, 22 and 43.

Health-related quality of life (HRQOL) assessment

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 (version 3.0) and head and neck cancer specific module EORTC QLQ-H&N35 were used to assess HRQOL. Following EORTC guidelines, the scores of the QLQ-C30 and QLQ-H&N35 items were linearly transformed to 0–100 scales. For functioning scales and the global HRQOL scales, higher scores correspond to better levels of functioning while for symptom scales, higher scores represent higher levels of symptoms or problems [15,16].

All patients were included in a prospective follow-up program, in which acute and late toxicity as well as HRQOL were assessed approximately 1 week before the start of radiotherapy, and at 6 weeks and 6, 12, 18 and 24 months after completion of radiotherapy.

Reference values for the QLQ-C30 and QLQ-H&N35 were available from previous work on development of speech and swallowing questionnaires, including a sample of 110 healthy volunteers recruited from the circle of family and friends of the group of researchers. The mean QLQ-C30 scores for this group of 110 volunteers were similar to those of a larger normative, representative sample of the Dutch general population reported recently by van de Poll-Franse et al. [17]. There are no QLQ-H&N35 data available from a larger sample of the Dutch general population. For this reason, we used the reference values from the sample of 110 volunteers for both the QLQ-C30 and QLQ-H&N35.

Statistics

Descriptive statistics were generated for the range of background and outcome variables. Differences between patient and reference group were tested regarding age (*t*-test) and gender (chi-square test). The primary outcome measures were the EORTC QLQ-C30 and the EORTC QLQ-H&N35 subscales. We classified sociodemographic and clinical variables categorically: age (<65 years vs. $\geqslant$65 years), gender, tumor subsite (oral cavity–oropharyx vs. hypopharynx–larynx), comorbidity (no–mild vs. moderate–severe), and survivorship (alive vs. died).

Linear regression analyses were used to test differences in HRQOL scores between patient and reference group, adjusted for age and gender. These analyses were performed at all time points, i.e. 6 weeks, and 6, 12, 18 and 24 months after completion of CRT. Furthermore, we adjusted the *p*-value with respect to each outcome for multiple testing by using Bonferroni correction, which resulted in a *p*-value of 0.05/6 = 0.008. Linearity and normality assumptions were checked using residual plots and were found satisfactory.

We used linear mixed-model analyses to assess the change over time in the patient group for the QLQ-C30 subscales global quality of life, physical, role, emotional, cognitive, and social function, pain, fatigue, and nausea-vomiting and for the QLQ-H&N35 subscales oral pain, swallowing, speech, senses, social eating, social contacts, and sexuality, linear mixed-model analyses were applied [18]. We built the models via several steps. First, we evaluated whether the course of HRQOL over time was linear or quadratic by adding a variable with time squared to the model. These models were compared on basis of the Maximum Likelihood fits and the Likelihood ratio test. Second, using the REML likelihood ratio test, we examined whether a random intercept and slope were necessary [19]. Third, we applied a forward regression technique to determine whether gender, tumor subsite, age, and comorbidity, as well as their interaction effect with time, were associated significantly ($p < 0.05$) with changes in HRQOL.

Since a large proportion of participants (38%) died during the course of the study, the missing at random assumption was probably not upheld. Therefore, we explored the need for a random effects pattern-mixture approach by accounting for differences in HRQOL over time between survivors and non-survivors. First, we built the statistical models as described above, in the completers group (i.e. survivors) only. Subsequently, we applied the final model in the non-completers (i.e. non-survivors) group only. As a last step, we applied the final model in the full dataset, and included a variable "dropout" – indicating whether a patient survived