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RADIOTHERAPY

Late toxicity, evolving radiotherapy techniques, and quality of life in nasopharyngeal carcinoma

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Abstract

Purpose To analyze quality of life (QoL) and functional state (FS) by patient-reported outcome (PRO) questionnaires (FACT-G, FACT-NP, PSS-HN, XeQOLS, and EQ-5D-3L) in long-term survivors nasopharyngeal carcinoma (NPC) treated with conventional radiotherapy (RT) and intensity modulated radiotherapy (IMRT).

Methods 25 patients answered to five questionnaires about QoL and FS. All patients were assessed also for late toxicity.

Results Functional Assessment of Cancer Therapy-General (FACT-G) and Performance Status Scale Head and Neck (PSS-HN) scores were significantly elevated (better QoL) in age <50 years ($p = 0.03$). PSS-HN score was higher in IMRT group. The observed xerostomia was lower in the IMRT group and in patients who received conventional RT had worse QoL according to XeQOLS (University of Michigan Xerostomia-Related Quality of Life Scale) score questionnaire. Lower PSS-HN score and higher XeQOLS score were significantly related with the late xerostomia ($p = 0.009$ and 0.002, respectively).

Conclusions Our preliminary data suggest that age, older techniques, xerostomia, and hearing loss are negative predictors of QoL.

Keywords Nasopharyngeal neoplasm · Quality of life · Radiotherapy · Xerostomia

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Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignancy in western countries, which arises from the epithelium of the nasopharynx. In Europe, its prevalence is about 1.4 per 100,000 inhabitants [1, 2]. Epstein Barr virus (EBV) is, with smoke, alcohol, and wood dust-related occupations, among the well-known risk factors for this tumor. Prognosis and association with EBV differentiate NPC from the other head and neck neoplasms [3–5]. Most stage I–II tumors are successfully treated by radical radiotherapy (RT), while patients with locoregionally advanced disease (stage III-IV) are cured by combined chemoradiotherapy (CRT) approach [6]. These treatments are related to high acute and late toxicities with impairment of patients' Quality of Life (QoL). Over the years, RT techniques evolved: Intensity Modulated Radiotherapy (IMRT), compared to the conventional bi-dimensional and tri-dimensional conformal RT (2D and 3D-CRT) achieved good tumor coverage, high tumor control rate, and effectively lowered the exposure dose of normal tissues around the tumor, reducing temporal lobe injury, xerostomia, hearing loss, trismus, cataract, retinitis, and damage to brain stem and optic chiasm. Traditionally, treatment evaluation has focused on objective measures like survival time, tumor recurrence, overall survival, or standardized toxicity [7–9], but few studies has evaluated a possible impact of treatment on health-related quality of life (HRQoL) and functional status (FS) in patients with head and neck cancer. Information from physician about expected HRQoL outcomes may help patients "to actively participate" in the medical decisions concerning their care [8]. There are a variety of QoL instruments (Patient-Reported Outcomes, PRO's) available in the field of head and neck oncology. In this study, we used five questionnaires to retrospectively analyze QoL, FS, and

their correlation to late toxicity, treatment, and patient-related parameters in long-term NPC survivors. [10–14]. The use of more questionnaires (each one focused on different aspects) allowed us to have a complete description of patients FS and QoL.

Materials and methods

Between January 1990 and December 2014, 56 patients with histologically proven NPC have consecutively been treated with RT alone or CRT at the Radiation Oncology Unit of the "San Donato Hospital" Arezzo. Patients stage was retrospectively defined according to the 7th edition of the International Union against Cancer (UICC) TNM classification from WHO [15]. The characteristics of the patients are shown in Table 1. Median dose was 70 Gy (range 60–70), using five fractions per week. In December 2014, at different time after therapy, 25 of 30 long-term NPC survivors completed five questionnaires on QoL and FS: FACT-NP (Functional Assessment of Cancer Therapy Nasopharyngeal Cancer Questionnaire), FACT-G (Functional Assessment of Cancer Therapy—General), XeQOLS (University of Michigan Xerostomia-Related Quality of Life Scale), PSS-HN (Performance Status Scale for Head and Neck Cancer), and EQ-5D-3L (Generic Multi-Attribute Instrument). The patients completed questionnaires during a medical visit. Late toxicity, evaluated in 25 NPC long

Table 1 Mean characteristics of 56 nasopharyngeal cancer cases

56 patients	
M/F	44/12
Median age	52.5 (range 18–83)
Stage	
I–II	13 patients (23%)
III–IV	43 patients (77%)
Neoadjuvant chemotherapy	14 patients (25%)
Radio-chemotherapy	36 patients (64.3%)
Radiotherapy alone	20 patients (35.7%)
2DRT	35 patients (62.5%)
3DCRT	12 patients (21.4%)
IMRT	9 patients (16.1%)
DSS	5 years 63.40%
	10 years 52.70%
LRRFS	5 years 70.20%
	10 years 66.90%
DMFS	5 years 76.20%
	10 years 72.70%
PFS	5 years 53.20%
	10 years 52.40%
OS	5 years 59.30%
	10 years 49.20%

survivors who responded to questionnaires, was scored according to Common Terminology Criteria for Adverse Event version 4.0 (CTCAE vs 4.0).

FACT-NP is a questionnaire that comprises a core questionnaire, FACT-G, and an additional concerns subscale, NasoPharyngeal Cancer Score (NPCS). FACT-G is a 27-item measure that is classified into four subscales, and is used to assess physical, social/family, emotional, and functional well-being. The NPCS consists of additional items specific of patients with NPC, such as eating, swallowing, mouth dryness, appetite, taste, voice quality, communication, appearance, pain, neck movement, tinnitus, hearing, vision, smell, and nasal blockage. Patients indicated their responses according to the last 7 days. For FACT questions, answers in the negative must be reversed and a higher score represents a better QoL or FS. Items are rated on a 5-point Likert scale. The total FACT-NP score is the sum of FACT-G and NPCS [16].

XeQOLS consists of 15 items and measures impact of salivary gland dysfunction and xerostomia on the four major domains of oral health-related QoL: physical, personal/psychological, social functioning, and pain/discomfort issues. Patients answered to questions by checking the box that describes best how true each statement was during the last 7 days (not at all, a little, somewhat, quite a bit, very much), with 1–5 scale. Higher scores represent greater degree of symptoms [17].

The PSS-HN is a validated clinician-rated instrument designed to evaluate performance in areas of functioning. It consists of three subscales assessing normality of diet, understability of speech, and eating in public. Each is rated from 0 to 100, with higher scores indicating a better performance [11].

The EQ-5D-3L descriptive system comprises the following five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems (level 1), some problems (level 2), and extreme problems (level 3) [18].

In this study, we analyzed if late toxicity was affected by different predictive factors (age, gender, stage, time elapsed from the end of treatment, RT techniques, and associated chemotherapy) and if it was significantly related to questionnaire scores about QoL and FS.

Statistical analysis

The Kaplan–Meier method was used to calculate the disease-specific survival (DSS), locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), progression free survival (PFS), and overall survival (OS) rates. DSS was measured from the end of RT to the date of death due to NPC or to the last follow-up evaluation. LRRFS and DMFS were measured from the date of the

end of RT to the date of the first observation of locore-
gional recurrence or distant metastasis, respectively. PFS
was measured from the date of the end of RT to the date
of the first observation of locoregional recurrence or dis-
tant metastasis or death due to NPC. OS was evaluated
from the date of the end of RT to the date of death or to
the last follow-up. The log-rank test was used to compare
the survival curves. The non-parametric Mann–Whitney U
test was used for QoL questionnaires analysis according to
late toxicity; the categorical data were analyzed using χ^2
test with Yate's correction. All calculations were performed
using IBM-SPSS® version 22.0 (IBM Corp., Armonk, NY,
USA, 2013). A two-sided p value < 0.05 was considered
significant.

Results and analysis

Survival and toxicity

Patients' features are summarized in Table 1. Male:female
ratio was equal to 3.5:1; age ranged between 18–83 years
(median 52.5). Median follow-up was 85 months (range
13–304). At the time of the analysis, no patient was lost
to follow-up, 23 (41.1%) died from disease, 3 (5.4%) died
from other causes, and 30 (53.5%) were alive. Twenty-nine
of them were disease-free and 1 patient had locoregional
relapse. In 23 dead patients, 10 (43.5%) had locoregional
relapse, 10 (43.5%) had distant metastasis, and 3 (13%)
had both locoregional recurrence and distant metastases.
In IMRT group, no recurrence was observed after an aver-
age follow-up of 30 months. In female patients, no metas-
tasis was recorded. Five and ten-year DSS, LRRFS, DMFS,
PFS, and OS are reported in Table 1. Age <50 years was
related to better DSS ($p = 0.009$), LRRFS ($p = 0.0004$),
and PFS ($p = 0.042$), while dose >66 Gy was related to
better LRRFS ($p = 0.012$) and PFS ($p = 0.048$); gen-
der (female) was associated with better DMFS and PFS
($p = 0.033$ and $p = 0.038$ respectively), as shown in Figs. 1
and 2. Concomitant chemotherapy showed a trend towards
better locoregional control ($p = 0.07$) but not better metas-
tasis-free survival. No significant association between
tumor stage, time elapsed from the end of treatment, and
outcome was observed. Table 2 shows the frequency of
the late toxicity by type and grade. Grade 1–2 late toxici-
ties were predominantly xerostomia (60%) and hearing loss
(32%). No G4 late toxicity was observed; G3 late toxic-
ity occurred in only three patients: one impaired vision,
one sensory neuropathy, and one subcutaneous fibrosis.
All cases of neuropathy occurred in patients treated in
the pre-IMRT era. IMRT had a downward trend of related
effects like neuropathy, otitis, and hypothalamic dysfunc-
tion ($p = 0.06$). We analyzed if different predictive factors
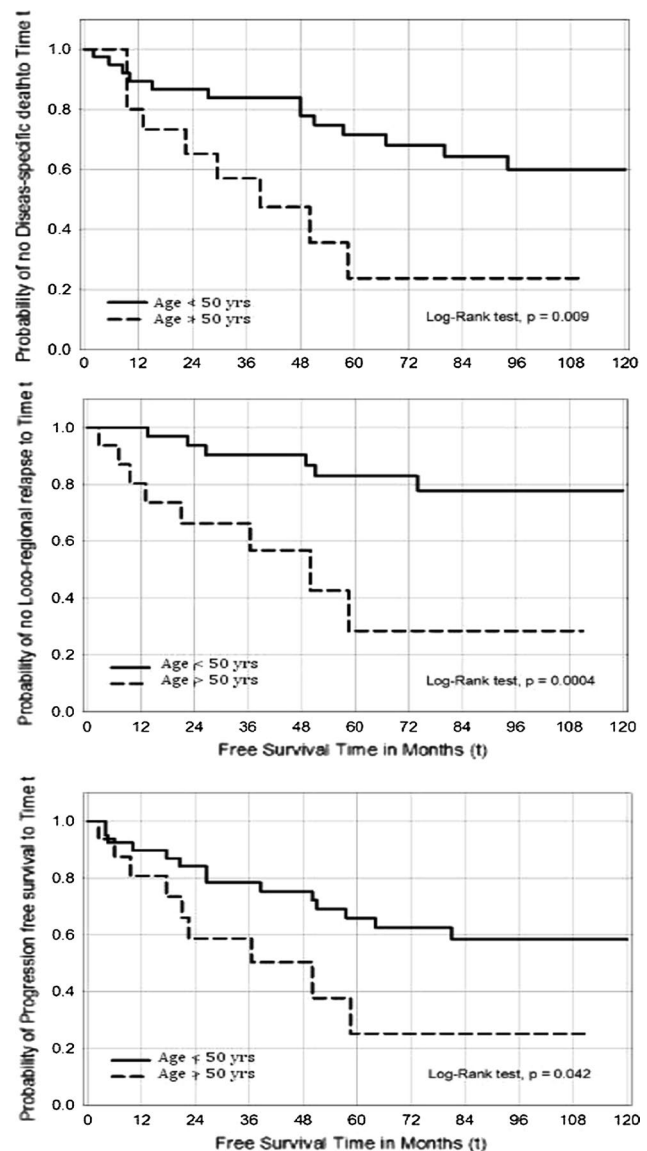
Fig. 1 Correlation between DSS (*up*), LRRFS (*middle*), PFS (*down*),
and age

influenced late toxicity. Only female gender was related to
fibrosis ($p < 0.01$).

Questionnaires

Five patients refused to answer the questionnaires for per-
sonal reasons. Of the 25 patients who completed ques-
tionnaires, 19 were men and 6 women aged 49.6 (range
18–87); 8 patients were treated 1–4 years before compil-
ing questionnaires and the remaining 17 received RT at
least 4 years before. Table 3 shows the score summary of
questionnaires. Table 4 reports the frequencies of problem
levels subdivided according to the EQ-5D-3L dimensions:
72% of cases had not problems about their cancer, 16% of

(A)

(B)
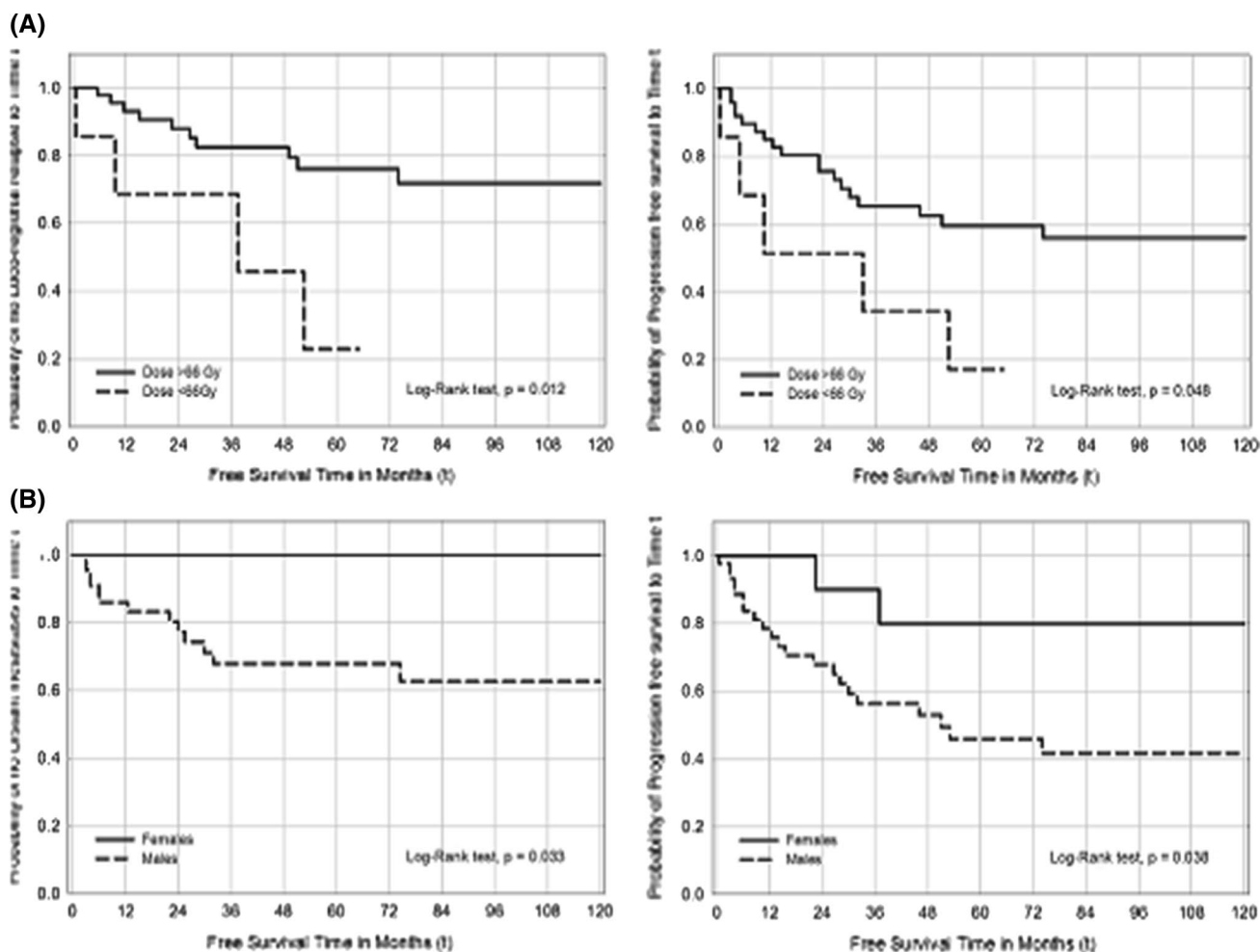
Fig. 2 Correlation between LRRFS (*left*), PFS (*right*), and dose; **b** Correlation between DMFS (*left*), PFS (*right*), and gender

Table 2 Late toxicity

Late toxicity	G1	G2	G3
Pain	5 patients (10%)	2 patients (3.5%)	–
Dysphagia	4 patients (7%)	4 patients (7%)	–
Mucositis	2 patients (3.5%)	–	–
Dysgeusia	5 patients (10%)	2 patients (3.5%)	–
Xerostomia	9 patients (16%)	19 patients (34%)	–
Hearing loss	20 patients (35%)		

Others (12.5%):1 patient: impaired vision G3, 3 patients: sensory neuropathy, 3 patients: fibrosis G2–G3

Table 3 Summary of QoL and functional status

Instrument	Median score	Range	Maximum score
FACT-NP	127	83–169	172
FACT-G	87	60–108	108
XeQOLS	31.07.00	16–59	60
PSS-HN			
Eating in public	100	25–100	100
Understandability of Speech	100	50–100	100
Normalcy of diet	90	30–100	100

cases had some problems, and 12% had severe problems, more frequently pain, or discomfort. Patients aged <50 had significant better QoL according to FACT-G and PSS-HN scores ($p < 0.03$). Moreover, a trend toward improved QoL in patients treated with IMRT was showed by PSS-HN and EQ-5D-3L scores ($p = 0.07$ and $p = 0.06$, respectively)

(Table 5). G1–2 late xerostomia was significantly related to lower PSS-HN and higher XeQOLS score ($p < 0.009$ and $p < 0.002$, respectively). Patients with G1–G2 xerostomia had also worse FACT-NP scores without reaching statistical significance. Hearing loss seemed to be related to worse PSS-HN score ($p = 0.06$) (Table 6).

Table 4 EQ-5D-3L dimension of health

	No problems n (%)	Some problems n (%)	Severe problems n (%)
Mobility	22 (88)	3 (12)	0 (0)
Self-care	21 (84)	3 (12)	1 (4)
Usual activities	18 (72)	6 (24)	1 (4)
Pain or discomfort	13 (52)	9 (36)	3 (12)
Anxiety or depression	16 (64)	8 (32)	1 (4)

Table 5 Correlation between questionnaires and prognostic factors

Questionnaire	Age p value	Gender p value	Technique p value	Conc. CT-RT p value	Time from treatment p value
FACT-G	0.03	0.4	0.2	0.6	0.1
PSS-HN	0.03	0.08	0.07	0.5	0.7
FACT-NP	0.07	0.7	0.2	0.5	0.4
EQ-5D-3L	0.39	0.2	0.06	0.7	0.8
XeQOLS	0.9	0.1	0.3	0.5	0.3

Table 6 Correlation between late toxicity and questionnaires

	FACT-G p value	FACT-NP p value	EQ-5D-3L p value	PSS-HN p value	XeQOLS p value
Xerostomia	0.5	0.06	0.2	0.009	0.002
Hearing loss	0.9	0.5	0.4	0.06	0.5
Neuropathy	0.9	1	0.6	0.9	0.1
Fibrosis	0.7	0.3	1	0.6	0.8
Others	0.5	0.7	0.7	0.3	0.5

Discussion

Inge et al. reported that, in NPC, sociodemographic parameters like younger age appeared to be preeminent predictors of both OS and DSS [19]. DSS, in our experience, was related to age (<50 years), LRRS to age and dose (>66 Gy), and PFS to age, gender (female), and dose. Fang et al. found that besides socio-economic levels, advances in RT technique played a significant role to improve QoL of NPC patients suggesting that QoL may be a prognostic indicator in NPC [20]. In our study, we used a combination of questionnaires, FACT-NP, FACT-G, XeQOLS, PSS-HN, and EQ-5D-3L, in patients with NPC to get more information about QoL and FS by disease-specific instruments. Our data suggested that patients aged <50 had a better QoL based on FACT-G and PSS-HN questionnaires. Some studies suggested that IMRT is associated with statistically significant improvement in several important QoL domain, including swallowing, dry mouth, and social eating [19, 21, 22]. Our study showed a trend between IMRT and better QoL according to PSS-HN and EQ-5D-3L questionnaires, without to reach statistical significance, probably due to the small number of patients analyzed. Bian et al. reviewed the published literature addressing the question of whether IMRT resulted in an improvement of QoL, especially xerostomia-related QoL. They found that IMRT improved QoL, but xerostomia-related items still had a significantly negative effect after 2 years from the end of treatment on survivors' QoL [23]. Severe xerostomia, neuropathy, hearing loss, otitis, and hypothalamic dysfunction have a negative impact on QoL according to Tsai et al. [24]. In our study, patients with G1-G2 xerostomia had worse FACT-NP scores, while hearing loss was related to worse PSS-HN score.

Although this study has several limitations, because it includes a small number of patients with heterogeneous treatments, no pre-treatment QoL data are available and post-treatment evaluation to assess QoL and late toxicity were obtained at only one date for all patients, a very few data are reported on literature about QoL of NPC long-term survivors.

Conclusions

Our preliminary data on PROs measures suggest that negative predictors of QoL in NPC patients are age, techniques, xerostomia, and hearing loss. Better QoL is probably achieved with IMRT. Prospectively studies with a larger sample are needed to confirm our findings.

Compliance with ethical standards

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest. This study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

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