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HEAD AND NECK

Radiotherapy for head and neck cancer in nonagenarian patients: a possible cornerstone?

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Abstract In the field of radiotherapy, there is very little scientific data on the management of nonagenarians, especially in patients aged 90 years or more and with head and neck cancer (HNC). We made one of the first retrospective study of the feasibility and safety of radiotherapy in this population with HNC. Records of radiotherapy coming from four health facilities were studied to include all nonagenarian patients with HNC in the last 10 years and who received radiation therapy. We analyzed patient characteristics and primary cancers, as well as objective of the treatment (curative or palliative), efficacy and toxicity. Twenty patients receiving radiotherapy were identified; mean age was 93.2 years (standard deviation 2.8). Treatment was given with curative and palliative intent in 40 and 60 % of cases, respectively. The most common primary tumors were tumors of the salivary glands (30 % of cases), oral cavity tumors (25 % of cases) and thyroid tumors (15 % of cases). Median total prescribed dose was 47.5 Gy (12–70 Gy). Median number of delivered fractions was 18.5 (2–35 fractions). All patients received intensive supportive care during radiotherapy. Toxicities were mild to moderate. Radiotherapy could not be completed for four patients (20 % of cases). One patient developed grade 1–2 delayed toxicities. At the last follow-up, only four patients (20 % of cases) were alive. Cancer was cause of death in most cases. Radiotherapy may be performed for the nonagenarians with HNC. The total dose and fractionation must be adjusted to optimize the tolerance. However, the prognosis remains very poor, cancer being the main cause of death. Research of geriatric vulnerabilities prior to any treatment, in the context of a comprehensive geriatric assessment, is still recommended to select patients for radiotherapy.

Keywords Head and neck cancer · Nonagenarian · Radiotherapy

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Introduction

The Western countries population is an aging population. Life expectancy in Europe at age 65 has increased by 3 years for men between 1980 and 2008 (13.1 vs. 16.1 years) and 3.2 years for women between 1980 and 2008 (16.3 vs. 19.5 years) [1]. We can observe the same trend in USA, with life expectancy at age 65 has increased by 4.3 years for men between 1970 and 2006 (13.1 vs.

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17.4 years) and 3.3 years for women between 1970 and 2006 (17 vs. 20.3 years) [2]. The number of persons aged 90 or more in the world has increased significantly over the last two decades: from 6.714 million people in 1995, their number rose from 12.15 million people in 2010 [3]. We should see an acceleration of the phenomenon in the coming years: in 2050, world population prospects estimate a number of 71.16 million people aged 90 years or older (medium fertility variant) [4] 0.18 % of head and neck cancers (HNC) are diagnosed among patients aged ≥75 years [5, 6]. In France in 2010, the estimated incidence of new cases of HNC was 14,200 people [5]. In relation to the total population, this is one of the highest incident rates in the world. Nevertheless, there are few data on the treatment of older patients with HNC cancer [7], and especially for nonagenarian patients. The main studies on this subject are small retrospective studies published over 10 years ago.

The management of a patient with head and neck cancer usually requires close cooperation between the surgeon, the medical oncologist and the radiation therapist. The risk/benefit ratio of each treatment should be carefully evaluated [8] in patients presenting most often significant comorbidities, and this is especially true among older patients [9, 10]. Surgical treatment is usually designed to achieve exeresis of the tumor with free margins [11, 12], complemented by a more or less extensive lymph node dissection, according to the results of the initial staging. This treatment should be as conservative as possible [13], so that the patient can maintain acceptable functions of phonation, swallowing and breathing.

Elderly patients may benefit from a curative surgical treatment like younger patients, however, this procedure requires a prior evaluation of comorbidities [9, 14, 15].Chemotherapy among patients suffering from HNC can be administered at induction in the context of large inoperable tumor or for the purpose of laryngeal preservation [16–18]. Concomitant chemo-radiotherapy is the standard treatment for inoperable stage III–IV HNC [19, 20] and after surgery for stage III–IV HNC at high risk of recurrence (positive margins, lymph node capsule rupture) [21, 22]. Chemotherapy remains feasible in patients with HNC [9, 23–25] and taking care to adjust the dose of chemotherapy depending on the initial clinical evaluation as well as liver and kidney function [9].

In the field of Radiotherapy (RT), this treatment can be initiated with curative or palliative intent, for both younger subjects than for older patients [7]. After surgical treatment of stage III or IV HNC, local or regional recurrences and distant metastases are common. The operation is then often supplemented by adjuvant radiotherapy [26, 27], but few data are available for older people. Elderly patients with locally advanced head and neck cancer can well tolerate chemoradiation with intensity-modulated radiotherapy and image-guided radiotherapy [25]. In the context of palliative radiation therapy, several studies have analyzed different treatment protocols, usually of short duration, with minimal toxicity and maintaining an acceptable quality of life [28, 29]. Among elderly patients, one study found that hypofractionated radiotherapy was widely used not only in the palliative situation, but also in some cases of curative treatment, which seems more controversial [30]. Apart from the study of Chargari et al. [31], few studies have analyzed the radiotherapy among nonagenarian patients.

The aim of the present study is to report our retrospective experience of 20 patients aged 90 years or older receiving RT. Feasibility, delivery modalities, and benefit of RT to these patients were also analyzed.

Methods

Patients' and tumors' characteristics

Two university hospitals (or similar) and two private centers participated in this retrospective study. Records from RT departments were analyzed to identify all patients who were aged 90 years or older and who were treated by RT for HNC over past decade. Patients' characteristics (age, gender, performance status and living place) were examined together with tumor stage. Patients did not benefit from an oncogeriatric assessment before beginning treatment.

All patients received intensive supportive care during the radiotherapy course (regular dietetic monitoring with systematical enteral nutrition by gastrostomy, treatment of pain and management of mucositis), depending on their nutritional status (weight loss, albuminemia) and expected toxicity (dose, target volumes). If necessary, gastrostomy was performed within 5 days before the beginning of radiotherapy procedure. No patients received prophylactic antibiotics. Full-strength Isocal (Sondalis ISO, Nestlé, Switzerland or equivalent) was administered, starting 48 h after gastrostomy placement. The feeding schedule was as follows: day 1, 100 ml every 4 h for five feedings; day 2, 200 ml every 4 h for five feedings; day 3, 300 ml every 4 h for five feedings; and all other days, 400 ml every 4 h for five feedings. The total Isocal dose was 2,000 ml (2,000 kcal) per day during the entire treatment period. Patients were allowed to drink clear fluids or additional oral diet.

Treatment details

The final objective of treatment was considered either as potentially curative or palliative, according to the medical decision when choosing on treatment. For patients treated with palliative intent, non-curative doses were chosen to decrease symptoms (treatment of tumor generating mass pain, local compression, dyspnea or bleeding). Therapeutic indications (decision of treating, treatment intent) were

taken by radiation oncologist and validated after multidisciplinary decision, but radiation oncologist alone usually decided irradiation doses. The following radiation treatment details were examined: total dose, radiotherapy duration, fractionation, and the use of concomitant radio sensitizers. Previous anticancer therapies were also collected. The total biologically equivalent dose (BED) in 2 Gy fractions (EQD2) was calculated for each patient, using the linear quadratic model and an $\alpha/\beta = 10$ Gy for tumors.

Data analysis

During the RT course, toxicity was evaluated each week using National Cancer Institute Common Toxicity Criteria (CTCAE v3.0 criteria), then regularly until last follow-up. Acute toxicity was assessed for each patient, whatever follow-up time. Late toxicity was defined as any toxicity occurring more than 6 months after the end of RT. Follow-up and survival times were calculated from the day of completion of RT. Efficacy and survival were analyzed for patients with at least 3 weeks of follow-up. Efficacy was defined differently depending on the treatment intent. In curative intent, we assessed local control at last follow-up. In palliative intent, we analyzed control of symptoms.

Results

Patients

A total of 20 patients aged 90 years or older, receiving RT for HNC, were identified in four institutions (two university hospitals or assimilated, one general public hospital, two private centers) from 2003 to 2013. Mean age was 93.2 years (standard deviation 2.8). Nine patients (45 %) had been treated in public health care centers and 11 patients (55 %) had been treated in private centers. The female to male ratio was 1.2, without difference in age between males and females. The patient's Performance Status (PS) was generally altered, with a PS at the initiation of RT of 2–4 in 50 % of them. Eleven patients (55 %) were living at home and nine patients (45 %) were living in institution. Patients' characteristics are given in Table 1.

Table 1 Characteristics of patients, tumors, and previous surgeries

Patients' characteristics	*n*	(%)
Number	20	(100)
Mean age (SD)	93.2	(2.84)
Gender		
Female	11	(55.0)
Male	9	(45.0)
PS		
0–1	10	(50.0)
2–4	10	(50.0)
Living place		
Home	11	(55.0)
Institution	9	(45.0)
Tumors' characteristics		
Primary site		
Salivary glands	6	(30.0)
Oral cavity	5	(25.0)
Thyroid	3	(15.0)
Paranasal sinuses and nasal cavity	2	(10.0)
Larynx	2	(10.0)
Oropharynx	1	(05.0)
Hypopharynx	1	(05.0)
Stage		
Localized (T1T2N0)	6	(30.0)
Locally advanced (T3T4 or N+)	11	(55.0)
Not reported	3	15.0
Previous surgery		
Yes	9	(45.0)
No	11	(55.0)

PS performance status, *SD* standard deviation

Tumor's characteristics and previous surgeries

The different types of HNC were distributed as follows: The most common primary tumors were tumors of the salivary glands (6 patients, 25 % of cases), including five patients with tumor of the parotid gland, followed with tumors of oral cavity tumors (5 patients, 25 % of cases), followed by thyroid tumors (3 patients, 15 % of cases), larynx tumors (2 patients, 10 % of cases) and paranasal sinuses—nasal cavity tumors (2 patients, 10 % of cases). All diagnoses of cancers were histologically confirmed, except for one patient, 95 years old, who presented with acute dyspnea and bleeding due to bulky thyroid tumor and who was irradiated before histological confirmation of diagnosis. Squamous cell carcinoma was found in 12 patients. Most patients (11 patients, 55 % of cases) presented with locally advanced disease (defined as a T3–4 or lymph node positive disease). Before starting radiotherapy, nine patients (45 % of cases) had already undergone surgery for their cancer and were receiving RT as adjuvant or salvage therapy. Among these operated patients, the majority had a locally advanced cancer. Tumor's characteristics and previous surgeries are developed in Table 1.

Treatment intent and radiotherapy parameters

During radiotherapy, 12 patients (60 % of cases) were treated with palliative intent and eight patients (40 % of cases) with curative intent. Among the nine patients who

Table 2 Radiotherapy parameters

Treatment intent and target volumes	*n*	(%)
Treatment intent		
Palliative	12	(60.0)
Curative	8	(40.0)
Target volumes		
Primary site	17	(85.0)
Lymph nodes	2	(10.0)
Primary site and lymph nodes	1	(05.0)
Dose, fractions and treatment duration	Median	(Min–max)
Dose		
Total dose (Gy)	47.5	(12–70)
EQD2 ($Gy_{\alpha/\beta=10}$)	49.4	(16–70)
Fractions		
Number of fractions	18.5	(2–35)
Dose per fraction (Gy)	2.85	(2–6)
Total treatment duration	36.5	

Gy grays, *EQD2* biologically equivalent dose in 2 Gy fractions, *min* minimum, *max* maximum

had received previous surgery as part of their treatment, radiotherapy was delivered with curative intent in five cases (55.5 %), vs. only in three of the 11 patients (27.3 %) who had received RT as only treatment. Main palliative objectives, as reported in medical records, were treatment of pain ($n = 4$) and/or hemostatic therapy ($n = 2$) and/or decompression ($n = 4$), and/or local control ($n = 2$). High megavoltage linear accelerators and conformal dosimetry were used for all treatments. Median total dose and median EQD2 were 47.5 Gy (12–70 Gy) and 49.4 $Gy_{\alpha/\beta=10}$ (16–70 $Gy_{\alpha/\beta=10}$). In details, median EQD2 was 32.5 $Gy_{\alpha/\beta=10}$ for patients treated with palliative intent, vs. 62.2 $Gy_{\alpha/\beta=10}$ for patients treated with curative intent ($p = 0.004$). Median dose received per fraction was 2.85 Gy (2–6 Gy) in the total cohort. Median dose per fraction was 2.2 Gy (2–3 Gy) in patients treated with curative intent vs. 3 Gy (2–6 Gy) in patients treated with palliative intent ($p = 0.04$). Median number of delivered fractions was 18.5 (2–35 fractions). Regarding target volumes of radiotherapy, the majority of patients (17 patients, 85 % of cases) received only irradiation of the primary site without lymph nodes irradiation. No concurrent chemotherapy was performed. The median total treatment duration was 25 days. These results are detailed in Table 2.

Efficacy

Median follow-up was 35 weeks (ranging from 20 days to 30 months). All patients were analyzed for efficacy (curative intent: 8 patients; palliative intent: 12 patients) (Table 3). Among all patients, at last follow-up, eight patients (40 % of cases) experienced a tumor control (defined as stable disease or partial or complete response) and 12 patients (60 % of cases) developed tumor relapse or progression. In subgroup analysis, 4 of 8 patients (50 % of cases) among the curative intent group showed a tumor control against only 4 of the 12 patients (33.3 %) in the palliative intent group.

Table 3 Follow-up and tumor control

Follow-up	*n*	(%)
Follow-up time (weeks)	35 (median)	0–130 (min–max)
Status at last follow-up		
Alive	4	(20)
Deceased	16	(80)
Not intended treatment disruption		
For toxicity	3	(15.0)
For patient's noncompliance	1	(05.0)
Tumor control at last follow-up		
Time to local progression (weeks)	22 (median)	0–65 (min–max)
Status at last follow-up		
Controlled	8	(40.0)
Tumor relapse or progression	12	(60.0)

min minimum, *max* maximum

Among patients with pharyngeal squamous cell carcinoma or nasosinusal carcinoma ($n = 12$), tumor control was obtained in five patients (41 %): two complete responses and one partial response. Among patients with cancer of the salivary glands ($n = 6$) and thyroid ($n = 3$), local control rates at last follow-up were 50 and 0 %, respectively. Local control rates were 18 % in patients receiving RT as primary treatment (2/11) and 67 % (6/9) in patients receiving RT as adjuvant or salvage therapy. Median time to progression was 22 weeks (ranging from 0 to 65 weeks).

Symptoms like pain were controlled until last follow-up in eight patients (66.6 %) receiving palliative RT. Four patients had to stop treatment prematurely: three patients (15 % of cases) due to radiation toxicity and one patient (5 % of cases) due to noncompliance.

Unfortunately, effects of RT on quality of life or autonomy could not be assessed from this retrospective analysis because of lacking data.

Toxicity

Five patients (25 % of cases) have developed no acute toxicity. Maximal acute toxicity was grade 1–2 in 13 patients (65 % of cases) and grade 3–4 in two patients (10 % of cases). The main toxicities were mucositis, epithelitis, xerostomia and taste loss. Ten patients had a follow-up

Table 4 Toxicity data

Criteria	*n*	(%)
Acute toxicity (CTCAE v3)		
Grade 0	5	(25.0)
Grade 1	1	(05.0)
Grade 2	12	(60.0)
Grade 3	2	(10.0)
Grade 4	0	(00.0)
Late toxicity (CTCAE v3)		
Grade 1–2	1	(10.0)
Grade 3–4	0	(00.0)
None reported	9	(90.0)

CTCAE v3 Common Terminology Criteria for Adverse Events v3.0

exceeding 6 months and were evaluated for long-term toxicity, according to CTCAE v3.0 Criteria. No late toxicity was noticed in nine patients (90 % of cases). One patients (10 % of cases) developed grade 1–2 delayed toxicities. Toxicities reported for this patient were fibrosis and chronic pain. Toxicity data are detailed in Table 4.

Survival

At the last follow-up, four patients (20 % of cases) were alive against 16 patients died (80 % of cases). Cancer (local progression) was the cause of death in eight patients (50 % of cases of deaths). Among patients whose primary diseases were the salivary, thyroid, and nasal cavity ($n = 11$), three patients (27 %) were alive at last follow-up (mean follow-up: 44 weeks).

Discussion

There are recommendations on the optimal radio therapeutic management of elderly patients [32], but few studies have analyzed the feasibility of radiotherapy in a nonagenarian population. Mitsuhashi et al. [33] have retrospectively examined the clinical efficacy of RT in 32 patients aged 90 years or older. The most common primary tumors were head and neck cancer (44 % of cases) and skin cancer (19 % of cases). The radiation response without any severe complication was observed in nine (90 %) of the 10 patients with head and neck cancer treated with curative intent who finished treatment. In the article by Ikeda et al. [34], a Japanese multicenter retrospective analysis was performed on 57 nonagenarian cancer patients and treated with radical radiotherapy. The results showed that this type of treatment can be performed after adapting the treatment field and dose, and in the context of adequate family support. Oguchi et al. [35] have examined clinical records of 27 patients aged 90 years or older and who received RT. Authors found that the age was not an independent criterion for modifying the strategy of RT. A larger study by Wasil and colleagues has analyzed the issue of RT in 183 cancer patients aged 80 years or older [36]. They found that RT could be safely administered with 77 % of patients being able to complete the prescribed therapy.

This study is one of the first focusing specifically on Head and Neck (HNC) cancers among nonagenarians. The results of the study showed a higher proportion of cancers of the salivary glands (30 vs. 4.5 %) and cancers of the oral cavity (25 vs. 14.1 %) in nonagenarians compared to younger subjects [37]. We also observed a lower proportion of larynx tumors (10 vs. 20.8 %) compared with what has been reported in younger patients [37]. More than half of patients (55 %) had locally advanced cancer at diagnosis, which may pose a therapeutic problem in these very elderly patients, often carrying significant comorbidities. Indeed, 50 % of nonagenarians had a performance status ≥ 2, which may partly explain the low proportion (45 %) of patients who underwent a surgical procedure before the start of radiotherapy. Most often, physicians are reluctant to propose an invasive treatment to them, particularly surgery when general anesthesia is required for exeresis or reconstruction. Non-standard treatments are more frequently observed in this type of fragile population [8, 38, 39].

Of the 12 patients receiving palliative radiotherapy, about one half (5/12 patients, 41.6 % of cases) were excluded from potentially curative radiotherapy due to poor performance status, or age, or because of the contraindication to surgery. The social environment and the place of living of the nonagenarians seem to have played an important role in the treatment protocol. The median number of treatment fractions (both curative and palliative treatment; 18.5 fractions, minimum 2–maximum 35) was lower in this population of patients aged 90 years or more compared to what is observed in a population of younger patients. The total dose and fractionation were chosen with intent to minimize acute toxicity. These specific schemes were also chosen to minimize the inconvenient of a long treatment, which generally is associated with tiring daily transportation. Moreover, we noticed that no patient has received concomitant chemotherapy. Altogether, these results show that physicians were very careful to potential acute toxicity and that this could have generated under-treatment.

About the toxicity and effectiveness of treatment among nonagenarians, we observed that, with an appropriate dose and fractionation, radiotherapy was relatively well tolerated: grade 3–4 acute toxicities were noted in 10 % of cases, essentially mucositis, epithelitis and xerostomia. These toxicities were manageable by a suitable medical treatment. No unusual toxicity was observed. Only one patient developed a grade 1–2 late toxicity (pain, fibrosis),

which seems quite acceptable. Preventing these toxicities by supportive care is very important: the introduction of enteral nutrition, regular mouth cares and treatment of pain are essential to the success of radiotherapy. Given data of the study, it is impossible to draw a firm conclusion regarding survival. Moreover, we could not compare this small group of treated patients with a group of patients who were not referred for radiotherapy. Nevertheless, radiotherapy has brought an undeniable clinical benefit in the group of curative patients with a tumor control equal to 50 % (4 of 8 patients). Obviously, the tumor control rate was lower in the group treated with palliative intent (4 of 12 patients, 33 % of cases), but the main goal among this group of patients who was symptom control was obtained in 8 of 12 patients (66 % of cases). At the last follow-up, most patients were deceased, cancer being the main cause of death. Radiotherapy treatment was stopped prematurely in four patients (20 % of cases). This is significant and raises the question of the proper vulnerability assessment before starting treatment among these very elderly patients. Indeed, the patients included in the study did not receive initial oncogeriatric assessment because geriatric skills were not available in our centers during the study. It has already been shown that geriatric assessment conducted in the oncology setting could be directly interventional, with the aim to help the physician to choose the best cancer treatment [40]. Some effective tools such as the Charlson comorbidity score [41] or geriatric 8 (G8) [42] are now increasingly being used and can help the radiotherapist to refine the methods of treatment, through an oncogeriatric integrative approach, quality of life is optimized. The need for a multidisciplinary team decision in consultation with the family and the patient should be also highlighted.

Conclusion

With regular lengthening of life expectancy, the population of nonagenarians is increasing in Western countries. Many questions arise about the optimal medical management of these very elderly patients. The results of this study demonstrated that radiotherapy can be performed in nonagenarian patients with a diagnosis of HNC, although it is frequently given with palliative intent. The dose and fractionation of treatment should be tailored to optimize tolerance. Intensive supportive cares also play a crucial role in the success of treatment. The age at itself is not a major factor for excluding patients from radiotherapy. However, before treatment, a comprehensive geriatric and supportive care assessment is essential with audit of the effectiveness on each patient after a period of 12 months of treatment.

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