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Feasibility of radiation therapy in patients 90 years of age and older: A French multicentre analysis

Cyrus Chargari [a,*], Guillaume Moriceau [b], Pierre Auberdiac [c,d], Jean-Baptiste Guy [b], Avi Assouline [e], Fabien Tinquaut [f], Alexander Tuan Falk [g], Houda Eddekkaoui [b], Aurélie Bourmaud [f], Yvan Coscas [e], Pierre Annede [a], Romain Rivoirard [b], Benoite Mery [b], Jane-Chloé Trone [b], Yves Otmezguine [e], Cécile Pacaut [b], Olivier Bauduceau [a], Lionel Vedrine [a], Yacine Merrouche [h], Nicolas Magne [b]

[a] *Medical and Radiation Oncology, Hôpital d'Instruction des Armées du Val-de-Grâce, Paris, France*
[b] *Radiation Oncology, Institut de Cancérologie Lucien Neuwirth, Saint Priest en Jarez, France*
[c] *Radiation Oncology, Clinique Claude Bernard, Albi, France*
[d] *Radiation Oncology, Centre Hospitalier, Rodez, France*
[e] *Radiation Oncology, Centre Clinique de la Porte de Saint Cloud, Boulogne-Billancourt, France*
[f] *Centre Hygée – Centre Régional de Prévention des Cancers, Institut de Cancérologie Lucien Neuwirth, Saint Priest en Jarez, France*
[g] *Departement of Radiation Therapy, Centre Antoine Lacassagne, Nice, France*
[h] *Medical Oncology, Institut de Cancérologie Lucien Neuwirth, Saint Priest en Jarez, France*

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Abstract ***Background:*** There are only scarce data on the management of patients aged 90 years or older with cancer, and more particularly on the place of radiation therapy (RT). We report the first large study on patients (pts) aged 90 years or older receiving RT.
Methods and materials: Records from RT departments from five institutions were reviewed to identify pts 90 years of age and older who underwent RT for various malignant tumours treated between 2003 and 2012. Tumours' characteristics were examined, as well as treatment specificities and treatment intent.
Results: 308 pts receiving 318 RT courses were identified, mean age was 93.2 years (standard deviation 2.8). Treatment was given with curative and palliative intent in 44% and 56%, respectively. Factors associated with a curative treatment were performance status (PS), place of life, previous surgery and tumour stage. Median total prescribed dose was 36 Gy (4–76 Gy). Hypofractionation and split course were used in 88% and 7.3%, respectively. Most toxicities were mild to moderate. RT could not be completed in 23 pts (7.5%). No long-term toxicity was

* *Corresponding author:* Address: Radiation Oncology, Hôpital d'Instruction des Armées du Val-de-Grâce, 74 Boulevard de Port Royal, 75005 Paris, France. Tel.: +33 (0) 1 40 5 45 58; fax: +33 (0) 1 40 51 46 70.
E-mail address: chargari-vdg@hotmail.fr (C. Chargari).

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reported. Median overall survival was 22.9 months (95CI: 15.5–42.7 months). Cancer was the cause of death in 8.7% and 46% of pts treated with curative and palliative intent, respectively. ***Conclusion:*** This study shows that RT is feasible for patients aged 90 years or more. PS, place of life and tumour stage were factors of the therapeutic decision. There is no reason to withdraw pts with good general health condition from potentially curative RT, provided that careful attention is paid to factors of toxicity and to geriatric vulnerabilities.

1. Introduction

Most developed countries have accepted the chronological age of 65 years as a definition of an older person. This definition is at least controversial and it is obvious that it does not adequately match with current epidemiological changes. In fact, mean life expectancy has continuously increased over the past decades in developed countries. According to the Centres for Disease Control and Prevention, life expectancy in 2011 was 78.7 years, cancer being the second most prevalent cause of death [1]. The French National Institute of Statistics and Economic Sciences (INSEE) estimates that there could be about 200,000 centenarians in France in 50 years [1].

Cancer is a significant cause of morbidity and mortality in the elderly population and an increasing healthcare issue [2]. Most patients (pts) 70 years of age or older have been traditionally excluded from clinical trials, and the optimal management of cancer in this population remains uncertain. An increasing number of studies suggest that radiation therapy (RT) is feasible and plays a major role in the elderly [3]. However, there are only scarce retrospective data on anticancer treatments in patients aged 90 years or older and no prospective study is available in this population. It is thus difficult to draw conclusions regarding the feasibility or the clinical benefit of RT in very old patients, who are particularly fragile, with frequent associated morbidities and poor medical condition. Consequently, physicians are frequently reluctant to treat these patients radically, and patients aged 90 years or older are frequently treated in a less aggressive fashion than their younger counterparts [4].

We report our retrospective experience of more than 300 patients aged 90 years or older receiving RT. Feasibility, delivery modalities and benefit of RT to these patients were also examined.

2. Materials and methods

2.1. Patients and tumours

Records from RT departments from five French institutions were reviewed to identify patients who underwent RT treated between 2003 and 2012 and aged 90 years or older: two university hospitals or assimilated (1/ Institut Lucien Neuwirth, Saint Priest en Jarez; 2/ Hôpital d'Instruction des Armées du Val-de-Grâce, Paris), two private centres (1/ Clinique Claude Bernard, Albi; 2/ Clinique de la Porte de Saint Cloud, Boulogne) and one public hospital (Centre Hospitalier de Rodez, Rodez).

Patients' characteristics (age, gender, living place and general health status) were examined, as well as tumour stage. As none of the centres involved in this study had oncogeriatric resource at this time, patients did not receive routinely an integrated oncogeriatric assessment before beginning therapy.

2.2. Treatment characteristics

Treatment intents were classified as potentially curative or palliative, according to the judgment of the physician at the time of therapeutic decision. The objective of palliative treatment was also examined, if available. The following treatment characteristics were examined: total dose, treatment duration, fractionation and the use of concomitant radiosensitisers. Previous anticancer therapies were also analysed. For each patient, the total biologically equivalent dose (BED) in 2 Gy fractions (EQD2) was calculated using the linear quadratic model and an alpha/beta = 10 Gy for tumours.

2.3. Data analysis

Toxicity was assessed weekly during the RT course using CTCAE v3.0 criteria (National Cancer Institute Common Toxicity Criteria), then at regular intervals until the last follow-up. All patients were analysed for acute toxicity, whatever the follow-up time. Late toxicity was any toxicity occurring more than 6 months after completion of RT. Follow-up and survival times were calculated from the day of completion of RT. Only patients with at least three weeks follow-up were analysed for effectiveness or survival. Effectiveness was defined according to the treatment intent. In curative intent, we examined local control at last follow-up. In palliative intent, we analysed the control of symptoms. Progression-free survival (PFS), overall survival (OS)

and cause specific survival (CSS) were analysed using the Kaplan–Meier method (log-rank test).

3. Results

3.1. Patients

From 2003 to 2012, 308 patients aged 90 years or older receiving RT for various primary malignant tumours were identified. Those patients accounted for 1% of about 30,000 patients treated in our institutions. For comparison, patients aged between 85 and 89 years accounted for about 2% of the total. The ratio of patients aged more than 90 years consistently increased over time, ranging from less than 0.3% in 2004 to 1.6% in 2012. We could not estimate the number of patients of more than 90 years who were not referred. Mean age was 93.2 years (standard deviation 2.8). Median age was 92.9 years.

The female to male ratio was 1.5, without difference in age between males and females. The general health status was frequently altered, with a performance status (PS) at the initiation of RT of 0–1 in 34% of them, according to the World Health Organisation classification. Most patients were living at home. Table 1 shows patients' characteristics at the time of RT course.

3.2. Tumours and previous therapies

Most frequent primary tumours were skin tumours (30%, mean age: 93.7 years), followed with breast carcinoma (16%, mean age: 92.1 years), urological tumours (14.6%, mean age: 92.3 years) and tumours of the digestive tract (13.3%; mean age: 92.9 years). There was no significant recruitment bias and these tumour types were the most frequent, whatever the institutions (Table 1).

All patients had a histologically confirmed diagnosis of cancer. Most patients (56%) presented with locally advanced (defined as a T3–4 or lymph node positive disease) or metastatic disease. At time of RT, 155 patients (50%) had previously received one or more anticancer treatment(s). Those included surgery of primary tumour in 108 patients (35.0%), hormone manipulation in 36 patients (11.7%), previous history of RT in eight patients (2.6%) and chemotherapy in seven patients (2.3%). Prior surgery had been delivered in 72% and 54% of patients treated with curative intent for a breast carcinoma and a skin tumour, respectively. Characteristics of tumours and previously delivered therapies are presented in Table 1.

3.3. Treatment intent

A total of 318 RT courses were delivered, including 141 treatments (44%) with curative intent (140 patients) and 177 treatments (56%) with palliative intent (168 patients). Discussion in multidisciplinary board was not required for patients who were referred for palliative radiotherapy and/or in the context of emergency. Although information was frequently lacking from medical records, about 50% of indications were discussed in a multidisciplinary meeting, mainly for curative patients.

Most frequent primary tumours treated with curative intent were skin tumours (42%), breast carcinoma (23%), anorectal carcinoma (11.4%), urological tumours (5.7%, including six bladder cancers and two prostate cancers), and head and neck tumours (4.3%).

Palliative objectives were the treatment of pain in 47 patients (39%), reduction of a tumour mass compressing a nervous plexus, lymph nodes areas, the spine or other organs in 23 patients (19%), haemostatic therapy in 32 patients (26%), local control in 19 patients (16%) and unreported in the remaining patients. In univariate analysis, the following factors were associated with a choice of a curative intent treatment: performance status ($p = 0.0006$), life at home ($p = 0.03$), a previous history of surgery ($p < 0.001$) and the stage ($p < 0.001$). At multivariate analysis, the performance status ($p = 0.018$) and stage ($p < 0.01$) were significantly associated with a curative intent RT. Place of life did not enter the multivariate model, because it was interconnected with performance status at correlation analysis (Table 2).

3.4. Treatment characteristics

All treatments were delivered using high megavoltage linear accelerators and conformal dosimetry. Median total prescribed dose and median EQD2 were 36 Gy (4–76 Gy) and 41.4 $Gy_{\alpha/\beta=10}$ (4.6–84 $Gy_{\alpha/\beta=10}$). To note, our calculations were performed with an alpha/beta ratio of 10. Although debated, the alpha/beta ratio is probably lower for some tumour types, such as prostate cancer. Consequently, total equivalent doses could be slightly underestimated, and more particularly when high doses per fraction were used. However, in this series, only five patients received prostate RT, mainly for palliation of symptoms. Most patients received hypofractionated RT (HFRT). Median dose per fraction was 3.8 Gy (1.5–12 Gy). Thirty-nine radiation courses (12.3%) were normofractionated and HFRT was used in 279 treatments (88%). Median number of delivered fractions was 10 (1–36 fractions). Split course was used in 7.3% of patients. Concurrent chemotherapy was delivered in only three patients (capecitabine, carboplatin and chloraminophene) and one patient received concurrent cetuximab. As shown in Table 3, median total dose, median total EQD2 and median number of fractions were higher for patients receiving treatment with curative intent, as compared with palliative treatments ($p < 0.00001$, $p < 0.00001$ and $p < 0.00001$,

Table 1
Characteristics of patients, tumours and previously delivered therapies.

	Total (%)	ILN	VDG	CCB	CHR	CPSC
Patients						
Number	308 (100)	78	28	90	46	66
Mean age	93.2	93.1	93.0	93.1	91.5	94.5
Gender						
Female	185 (60)	49	16	45	31	44
Male	123 (40)	29	12	45	15	22
PS						
0–1	107 (35)	40	12	30	9	16
2–4	198 (64)	36	16	60	37	50
NR	3 (1.0)	2	1	0	0	0
Living place						
Home	178 (58)	45	6	60	25	38
Institution	104 (34)	25	4	30	21	28
NR	26 (8.4)	8	18	0	0	0
Tumours						
Primary site						
Skin	93 (30)	21	7	31	18	16
Breast	48 (16)	14	5	9	7	13
Urol	45 (5)	7	5	16	5	12
GI	41 (13.3)	12	2	9	8	10
H&N	23 (7.4)	9	1	8	3	2
Gynaecol	20 (6.6)	4	2	6	2	6
Haematol	17 (5.5)	9	2	4	1	1
P&P	13 (4.2)	1	1	5	2	4
Others	8 (2.6)	1	3	2	0	2
Stage						
Localised	65 (21)	13	7	24	10	11
LA	18 (38)	11	4	47	17	39
Metastatic	54 (18)	14	7	8	10	15
Not available	71 (23)	40	10	11	9	1

CCB: Clinique Claude Bernard; CHR: Centre Hospitalier de Rodez; CPSC: Clinique de la Porte de Saint Cloud; ILN: Institut Lucien Neuwirth; VDG: Hôpital d'Instruction des Armées du Val-de-Grâce.
GI: gastrointestinal; Gynaecol: Gynaecological; Haematol: haematological malignancies; P&P: pleural and pulmonary cancers; H&N: head and neck; LA: locally advanced; NR: not reported; PS: performance status; SD: standard deviation; Urol: urological tumours.

Table 2
Factors that influence the decision of a potentially curative RT.

	Odd ratio [95% confidence interval (CI)]	*p* Value
Univariate analysis		
Gender	1.53 [0,96; 2.43]	0.1
Performance status (0–1 versus 2–4)	2.37 [1.47; 3.84]	0.0006
Age	–	0.95
Stage (localised versus locally advanced)	4.17 [2.11; 8.25]	<0.001
Stage (localised/locally advanced versus metastatic)	65.02 [8.8; 480.69]	<0.001
Place of life (institution versus home)	0.55 [0.34; 0.91]	0.03
Multivariate analysis[*]		
Performance status (0–1 versus 2–4)	1.91 [1.12; 3.27]	0.018
Stage (localised versus metastatic)	148.75 [18.9; 1173.1]	<0.001

[*] Place of life was interconnected with performance status and did not enter the multivariate model.

respectively). Normofractionation was used more frequently for curative treatments ($p < 0.01$).

3.5. Effectiveness

Seventy-nine patients (26%), mainly treated with palliative intent, did not receive any follow-up from their radiation oncologist after completion of RT. A total of 207 patients were judged analysable for effectiveness (curative intent: 103 patients; palliative intent: 104 patients) (Table 4). In this subgroup, the mean follow-up time was 9.2 months (ranging from 0 to 5.4 years).

At the last follow-up, 56 patients who received curative treatment (54%) experienced complete response,

Table 3
Patients, tumours and treatment characteristics according to treatment intent.

Treatment characteristics	All pts	Curative	Palliative	*p* Value
Number of treatment courses	318	141	177	–
Median dose (Gy)	36 (4–76)	44.5 (11.5–76)	30 (4–65)	<0.00001
Median EQD2 ($Gy_{\alpha/\beta=10}$)	41.4 (4.6–84)	48.9 (11.5–84.2)	32.5 (4.7–84)	<0.00001
Median dose/fraction (Gy)	3.8 (1.5–12)	3 (1.7–9)	4 (1.5–12)	0.06
Number of fractions	10 (1–36)	12.5 (4–35)	6 (1–36)	<0.00001
HFRT rate (*n*;%)	279 (87.7)	(82.9)	(91.4)	<0.01

EQD2: biologically equivalent dose in 2 Gy fractions; Gy; Grays; HFRT: hypofractionated radiotherapy; NS: not significant; PS: performance status; pts: patients.

Table 4
Effectiveness data.

Analysable patients	207
Tumour control in curative pts	($n = 103$)
Complete response	56 (54)
Partial response	7 (6.8)
Stable disease	12 (11.7)
Progression	21 (20)
Including local progression	17 (17)
Not reported (NR)	7 (6.8)
Symptoms in palliative pts	($n = 104$)
Controlled until last follow-up	72 (69)
Progression before last follow-up	32 (31)

pts: patients.

Table 5
Toxicity data.

Criteria	Analysable pts	Curative	Palliative
Number of patients	308 (100)	140 (100)	168 (100)
Acute toxicity			
Grade 0	170 (55)	58 (41)	112 (67)
Grade 1–2	120 (39)	73 (52)	47 (28)
Grade 3–4	17 (5.6)	9 (6.4)	8 (4.7)
Grade 5	1 (0.2)	0 (0)	1 (0.6)
Late toxicity	87 (100)	42 (100)	45 (100)
Grade 0	74 (85)	34 (81)	39 (87)
Grade 1–2	13 (14.9)	7 (17)	6 (13.4)
Grade >2	1 (1.1)	1 (2.3)	0 (0)

pts: patients.

seven patients (6.8%) experienced partial response, 12 patients (11.7%) had their disease stable and 21 patients (20%) experienced tumour progression, including 17 patients with local progression (17%) within a median time interval of 22 weeks (from 0 to 22 months). Tumour control was unspecified in seven patients (6.8%).

When detailing effectiveness for most frequent primary tumours treated with curative intent, complete responses, partial responses and stable diseases were observed in 28 (62%), 2 (4.4%) and 2 (4.4%) out of 45 patients with skin tumours, in 16 (64%), 2 (8%) and 4 (16%) out of 25 breast cancer patients. No local progression was reported for both tumour locations.

Progression of local symptoms in the course of the disease was seen in 32 patients (30.7%) treated with palliative intent. Median time from RT completion to progression of symptoms was 17 weeks (from 0 to 20 months). Four patients experienced immediate progression of their symptoms despite palliative RT. Symptoms were controlled until last follow-up in the remaining 72 patients (69.3%) receiving palliative RT. The latency to see any effect could not be investigated, because of lacking data.

3.6. Toxicity

There was no acute toxicity in 170 patients (55.2%). Maximal acute toxicity was grade 1–2 in 120 patients (39%), grade 3–4 in 17 patients (5.6%) and grade 5 in one patient (0.2%). RT could not be completed in 23 patients (7.5%). Underlying causes were: local toxicity ($n = 8$), decrease of general health status ($n = 6$), death from cancer during RT course ($n = 1$), patients' non-cooperation ($n = 2$), unrelated cardiac event ($n = 1$) and unspecified ($n = 4$). One patient died from treatment-related peritonitis.

Eighty-seven patients (28%) had a follow-up exceeding 6 months and were thus assessable for long-term toxicity. No delayed toxicity was reported in 74 patients (85%). Grade 1–2 delayed toxicity was reported in 13 patients (14.9%). One patient experienced grade 3 toxicity (1.1%). Toxicity data are detailed in Table 5.

3.7. Survival

A total of 207 patients were analysable for survival. The median OS estimated from the Kaplan–Meier curves was 22.9 months (95confidence interval (CI): 15.5–42.7). In details, median estimated OS was 51.9 months in patients treated with curative intent (95CI: 35.9–not reached) and 13.8 months in patients treated with palliative intent (95CI: 8.9–22.9). Median estimated CSS was 26.2 months in the whole group, 62.1 months (51.9–not reached) in patients receiving curative RT, and 13.9 months in patients receiving palliative RT (95CI: 8.9–23.6). Median PFS was not reached in both groups. At last follow-up, 67 patients (32%) were deceased, including 17 patients receiving

Table 6
Causes of death in patients analysable for survival.

	All pts	Curative	Palliative	*p* Value
Analysable pts	207 (100)	103 (100)	104 (100)	–
All causes of death	67 (32)	17 (18)	50 (48)	$p \leqslant 0.001$
Cancer	53 (26)	9 (8.7)	44 (46)	$p \leqslant 0.01$
RT-induced toxicity	1 (0.5)	0 (0.0)	1 (1.0)	
Unrelated causes	8 (3.9)	4 (3.9)	4 (3.9)	NS
CV event	6 (2.9)	3 (2.9)	3 (2.9)	NS
Sepsis	1 (0.5)	1 (1.0)	0 (0.0)	NS
Bowel occlusion	1 (0.5)	0 (0.0)	1 (1.0)	NS
Suicide	1 (0.5)	0 (0.0)	1 (1.0)	NS
Unspecified	4 (2.0)	4 (3.9)	0 (0.0)	NS

CV: cardiovascular; NS: not significant; pts: patients; RT: radiotherapy.

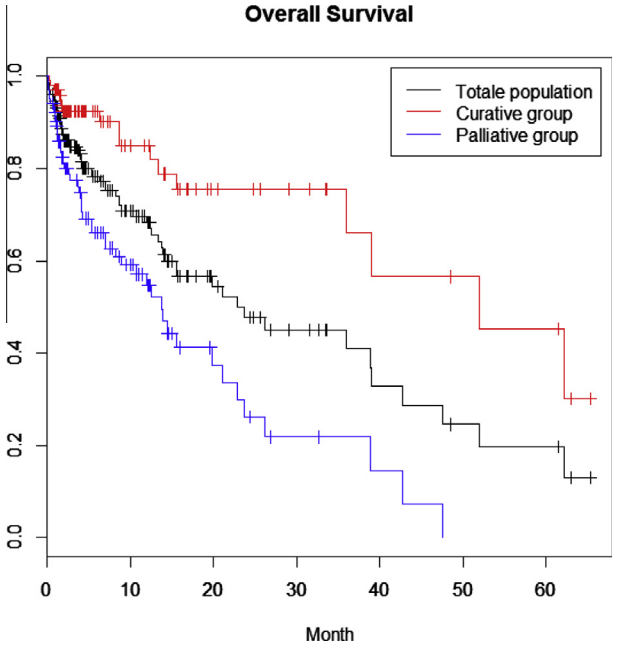

Fig. 1. Kaplan–Meier curves of the estimated overall survival, according to the treatment intent.

RT with curative intent (18%) and 50 patients receiving RT with palliative intent (48%). Cancer was the cause of death in 8.7% of patients receiving RT with curative intent and in 46% of patients receiving RT with palliative intent ($p \leqslant 0.01$) (Table 6). Kaplan–Meier curve of the estimated overall survival, according to the treatment intent, is shown in Fig. 1.

4. Discussion

Most data published regarding the optimal management of elderly patients refer to patients aged 70 years or more [5]. Vulto et al. have investigated primary RT use according to age in two RT departments in the Southern Netherlands. Only 20% of patients aged 75 or older received primary RT [6]. In 2006, same authors had shown that age was a stronger predicting factor over whether patients received RT or not. Patients aged 65 years to 80 years or with comorbidities received more frequently RT alone, compared with younger patients and patients without comorbid conditions [7].

This is the first large cohort study that investigates the issue of RT in patients aged 90 years or more. The choice of reporting about this selected group of age was based on the very limited knowledge we have on this population, which will probably continuously increase over next years because of population ageing. Patients aged 90 years or more have their diagnosis of cancer made at a late stage of the disease and receive frequently non-standardised therapies [8–10]. Few studies including only a low number of patients have suggested that RT was feasible, with tolerable acute side-effects [11–16]. A study by Wasil and colleagues have examined the issue of RT in 183 cancer patients 80 years of age and older. They found that 77% of patients were able to complete the prescribed therapy [14].

We examined the benefit of treatment in this very particular subgroup of patients, who have exceeded their life expectancy. In fact, the decision to treat these patients raises ethical issues and medico-economic questions that could not be resolved here. This analysis includes patients with various tumours receiving heterogeneous treatments and consequently, it does not allow drawing standard strategy. Repartition of primary tumours differed in these patients from their younger counterparts. In our population, skin tumours accounted for the most frequent tumour type, with patients frequently presenting with a locally bulky disease being symptomatic. Consistent with previously published data, patients presented at a late stage of disease, when radical surgery has become unfeasible.

Although it is uncertain whether this study adequately reflects practice among radiation oncologists, it seems that a significant number of potentially curative patients will receive only palliative care or suboptimal therapeutic sequence. In this series, about one half of patients (46%) receiving palliative RT was excluded from potentially curative RT because of age or general health status or contraindication for a standard surgery. Beyond the choice of treatment intent, RT should be individualised to the tumour stage and location, and to the general status of the patient. The social environment and the patients' decision should also be taken into account. There was no evidence from medical records that the irradiation technique was changed because of age, but total dose and fractionation were chosen with intent to minimise acute toxicity. Although the information was not available, it is probable that target volumes were also minimised for decreasing side-effects. We observed that split course was used in a relatively low number of patients (lower than expected in this age group).

More than 80% of patients treated with curative intent RT received HFRT, which allows to deliver a

treatment that is as comfortable as possible and is frequently used in elderly patients [17,18]. HFRT was found as effective as more protracted RT schemes for palliation of symptoms related to tumour disease. Although high doses per fraction could theoretically increase the risk of late sequels, an iso-effective and iso-toxic schedule can be obtained by lowering the total dose, as was evidenced provided by clinical trials in breast carcinoma. Long-term toxicity is not really a relevant concern in this population. However, some curative patients were long-term survivors. Other factors of acute toxicity, such as total dose and concurrent agents, were also very carefully considered in these patients. Median EQD2 was below 50 $Gy_{\alpha/\beta=10}$ and concurrent chemotherapy delivered in combination with RT in only one patient. Altogether, these findings show that physicians were very careful to potential toxicity and that this anxiety of potential toxicity generates under-treatment.

One unexpected finding was that about one quartile of patients did not receive any follow-up from their radiation oncologist. This does not preclude that patients were readdressed to their medical oncologist, geriatrist, organ specialist or general practitioner. This probably also reflects reluctance of radiation oncologists to generate disagreement to these elderly patients who are usually not eligible to salvage surgery or systemic therapy.

The definitive impact of RT on patients' autonomy and quality of life or pain could not be determined. Given heterogeneity of tumours, it was also impossible to draw any firm conclusion regarding survival data. However, RT conferred clinical benefit in most patients treated with curative intent. In the same way, overall survival in these patients exceeded four years. In the palliative setting, there was frequently missing information regarding effectiveness, but it seemed that more than half of patients had no progression of their symptoms until the last follow-up. Although radiotherapy was rather well tolerated, probably in part because of the lower total dose, treatment disruption was observed in about 7.5% of patients, which might reflect an insufficient analysis of geriatric vulnerabilities before RT decision. In fact, geriatric competence was not available in our centres at the time of the study, and consequently patients did not receive appropriate oncogeriatric assessment. A systematic use of oncogeriatric scales, such as the Charlson comorbidity score [19] or the Cumulative Illness Rating Scale [20], is now strongly encouraged to better pay attention to comorbidities. It was shown that a geriatric consultation with comprehensive geriatric assessment could change the final therapeutic decision in elderly cancer patients [21].

In 2009, Vulto et al. have assessed the knowledge of palliative RT through questionnaires sent to 1100 general practitioners in the area of the Comprehensive Cancer Centre South in the Netherlands. Analysis of 498 questionnaires showed that knowledge of palliative RT was good on bone metastases and spinal cord compression, but poor about other palliative indications [22]. This survey led to postgraduate training suggesting the potential of radiotherapy, especially in the very old. Such an approach should be also conducted in France for improving the management of elderly patients with cancer.

5. Conclusion

This study shows feasibility of RT in patients aged 90 years or more, provided that an adequate irradiation scheme is chosen. The age by itself should not be a determining factor for excluding patients from RT. However, tumour stage, general health status and the choice of patient should be taken into account in the therapeutic decision. When an appropriate treatment is delivered, RT is associated with rather low toxicity, high effectiveness and satisfactory survival. There is no doubt that this population will increase over the next years, justifying further questioning on the optimal treatment in these very old patients, according to the tumour type, to the stage and to patients' general health status. The choice of optimal should include an accurate assessment of geriatric vulnerabilities for ensuring that patients will receive a treatment with a favourable therapeutic index.

Conflict of interest statement

None declared.

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