Journal of Nuclear Medicine & Radiation Therapy

Jihan et al., J Nucl Med Radiat Ther 2018, 9:4
DOI: 10.4172/2155-9619.1000373

Research Article Open Access

Treatment Compliance and Radiation Associated Toxicities in Old Versus Young Patients: Prospective Comparative Case-Control Study

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Received date: July 13, 2018; **Accepted date:** August 28, 2018; **Published date:** September 06, 2018

Abstract

Background: There are only few data on treatment compliance and radiation associated toxicities that occurred in old patients with cancer undergoing radiation therapy. The aim is to learn more about treatment compliance and adverse events that occurred during radiotherapy in elderly subjects compared to young subjects.

Methods: Our work is a prospective case-control study, conducted between January and November 2016. Included patients underwent radiation therapy with curative intent for various malignant tumours. 242 Patients were separated into 2 groups, according to age (cut-off 65 years). Patients and tumours characteristics were examined as well as treatment specificities. The two groups were compared in terms of treatment related toxicities and treatment compliance. Radiation associated toxicities were assessed weekly during the radiotherapy.

Results: The age distribution of the group "old patients" and "young patients" was 72.4 ± 5 and 48.4 ± 8.6 respectively. There was no significant difference in terms of toxicities according to the age group. For old patients, maximal acute toxicity was grade 3–4 in 20 patients (17%) and for young patients maximal acute toxicity was grade 3–4 in 26 patients (21%). For treatment compliance, a statistically significant difference was found between old and young patients. For old patients, the scheduled RT course was completed by 96 patients (81.3%) In the other group, RT course was completed by 116 patients (93.5%). For old patients living place, dose of radiotherapy and toxicity grade were associated with good compliance and for young patient only sex was associated with good compliance.

Conclusion: Age alone should not be considered independently. Living condition as well as the prescribed dose should be assessed and incorporated into treatment plans.

Keywords: Radiation therapy; Treatment toxicity; Curative cancer; Chemotherapy; Conformal dosimetry; Mutltivariate analysis; Univariate analysis

Abbreviations: AJCC: American Joint Committee on Cancer; PS: Performance Status; ECOG: Eastern Cooperative Oncology Group; SD: Standard Deviation; CCI: Charlson Comorbidity Index; CTCAVE v 3.0 criteria: Common Terminology Criteria for Adverse Events Version 3.0; IQR: Interquartile Range; NCCN: National Comprehensive Cancer Network; RT: Radation Therapy

Introduction

The aging of the population is a global phenomenon. The population over sixty is growing rapidly, reflecting improving health and socio-economic conditions, but it also brings particular health challenges [1].

In Morocco, the elderly will represent 15.4% of the total population by 2030 and 23.2% by 2050, which is twice the current rate according to the population projections of the High Commissioner for Planning [2]. Since most tumors are age dependent, healthcare of this vulnerable population will be of a great challenge.

In fact, medical care requires in addition to treatment delivery, several aspects of social support for this category of patients including transportation, home caregiving to achieve timely help in case of serious complications during treatment, as well as psychological support, so that old patients can obtain full course regimens and optimal benefits from therapy [3].

In old patients, radiation therapy (RT) stands among treatments of first intent in curative cancer therapy [4]. Few available data from the literature indicate that RT can be highly effective and well tolerated, so that age alone should not be a limiting factor in old patients with cancer [5,6].

Recommendations for or against RT should be established by a comprehensive, personalized risk-benefit assessment that evaluates the expected treatment efficacy and toxicity. Which means that an optimal risk-benefit ratio guaranties a maximal treatment efficacy (as determined by locoregional control, survival, and cancer-related symptom management) and simultaneously minimal treatment toxicity [7].

Clinicians should be aware of both the potential to over treat elderly patients with significant competing non cancer mortality risk as well as the potential to under treat patients. Under treatment can result either from underestimating the patient's real life expectancy or from underestimating the aggressiveness of the cancer [8]. Because of old patients are generally excluded from trials [9-11], there are few data on the effects and toxicity of radiotherapy in this age group so there is a clear need to address the particular aspects of this specific patients group.

The aim of our work is to learn more about the treatment compliance and adverse events that could occur during radiotherapy with curative intent in elderly patients compared to young ones.

Materials and Methods

Study design

It is a single center prospective case-control study, conducted between January and November 2016. European Organization for Research and Treatment of Cancer considers 65 year old as a cutoff for the definition of old patients. In our study patients were separated into 2 groups:

Case group A: Patients aged over 65 years, who have been diagnosed with cancer, admitted in our department to receive curative treatment by RT with or without concomitant chemotherapy. RT may be exclusive, neoadjuvant or adjuvant to chemotherapy or to surgery.

Control group B: Patients aged between 18 and 65 years, who received curative RT in the same period.

Patients and treatment characteristics

We examined patients characteristics including age, gender, living condition (family or alone), co morbidity and medication (number of drugs <3 or ≥ 3), tumour stage according to AJCC cancer staging [12], performance status (PS) as defined by the Eastern Cooperative Oncology Group (ECOG) [13] (0=optimum performance status, 4=worst performance status) [13].

patients with an ECOG score of 0 to1 were categorized as having good performance status, and those with a score of 2 to 4 were categorized as having moderate to poor performance status.

We also examined irradiated sites (head and neack, trunk or abdominopelvic), total dose, treatment duration, the use of concomitant chemotherapy (yes or no), treatment toxicity and treatment compliance.

Several comorbidity indexes are used in geriatrics, in our study we used Charlson Comorbidity index (CCI) [14].

In clinical practice, the CCI reduces comorbidities into a single numeric score that enable health professionals stratify patients into subgroups based on disease severity.

The CCI has moderate to good inter-rater reliability of 0.74 to 0.945 in older cohorts with cancer [15,16]. Each old patient in our sample was scored according to CCI.

The following treatment characteristics were also examined

For all patients we watched the occurrence of acute toxicity and treatment adherence (completed, interrupted stopped course). Patients who had complete scheduled RT without interruption were categorized as having good compliance, and those who interrupted or stopped treatment were categorized as having moderate to poor compliance.

Toxicity was assessed weekly during the RT course using CTCAE v3.0 criteria (Common Terminology Criteria for Adverse Events) [17] by the same physician.

Patients with grade 2 acute toxicity or less were scored as low grade toxicity, the other patients who developed grade 3 or 4 acute toxicity were scored as high grade toxicity.

Statistical Analysis

A sub-categorization of "younger old" (65-75 years), "older old" (75-85 years) and " the oldest old" (≥ 85 years) has been introduced to allow allocation of elderly patients with cancer [18].

The statistical analysis was performed in three steps. Firstly, descriptive statistics were calculated for baseline characteristics primary for all patients and secondary for each group of patient's group, "old patients" group and "young patients" group defined according to the recommendations described above.

For variables that were normally distributed, the mean ± SD was reported. For dichotomous variables, the number (%) of patients was listed relatively to the total number of patients for whom information about the characteristics under investigation were available.

Then, we performed univariate and multivariate analysis for the whole series and for each group. We carried out several analyses between the different groups of patients.

Categorical variables were analyzed using t-Student test and chi-square or Fisher's test as appropriate and the odds ratios with 95% confidence intervals were calculated.

Factors found to be significant ($p<0.20$) in univariate analysis were included to the multivariate model. These analyses were performed using SPSS 13.0. P-Values<0.05 were regarded as significant.

Results

Characteristics of cases and controls

From January to September 2016, 242 patients receiving curative RT for various primary malignant tumours were identified. Group A and group B included 118 cases and 124 controls respectively.

For the whole sample the general health status was conserved with a performance status at the initiation of RT of 0–1 in 96.7% (n=234) according to ECOG. 95.9% of the patients were living with family. Table 1 shows patient characteristics at the time of RT course.

	Total (N=242), n (%)	Old patients (N=118), n (%)	Young patients (N=124), n (%)	p value
Age (years), mean ± SD	60.1 ± 13.9	72.4 ± 5	48.4 ± 8.6	

Gender, n (%)				
Male	82 (33.9%)	48 (40.7%)	34 (27.4%)	0.02
Female	160 (66.1%)	70 (59.3%)	90 (72.6%)	
Living condition, n (%)				
With family	232 (95.9%)	110 (93.2%)	122 (98.4%)	0.04
Alone	10 (4.1%)	8 (6.8%)	2 (1.6%)	
Number of drugs, n (%)				
<3	224 (92.6%)	102 (86.4%)	122 (98.4%)	<0.001
≥ 3	18 (7.4%)	16 (13.6%)	2 (1.6%)	
Performance status, n (%)				
ECOG (0 or 1)	96.7% (n=234)	94.9% (n=112)	122 (98.4%)	0.13
ECOG (≥ 2)	3.3% (n=8)	5.1% (n=6)	2 (1.6%)	
Tumor site, n (%)				0.11
Head and neck cancer	56 (23.1%)	26 (22%)	30 (24.2%)	
Nasopharyngeal cancer	36 (14.8%)	14 (11.8%)	22 (17.7%)	
Laryngeal cancer	12 (5%)	6 (5.1%)	6 (4.8%)	
Other	8 (3.3%)	6 (5.1%)	2 (1.6%)	
Trunk cancer	100 (41.3%)	46 (39%)	54 (43.5%)	
Breast cancer	62 (25.6%)	26 (22%)	36 (29%)	
Lung cancer	32 (13.2%)	16 (13.6%)	16 (12.9%)	
Oesophagus cancer	6 (2.5%)	4 (3.4%)	2 (1.6%)	
Digestive cancer	14 (5.8%)	10 (8.5%)	4 (3.2%)	
Gastric cancer	8 (3.3%)	6 (5.1 %)	2 (1.6%)	
Gynecological cancer	62 (25.6%)	28 (23.7%)	34 (27.4%)	
Cervical cancer	60 (24.8%)	28 (23.7%)	32 (25.8%)	
Endometrial cancer	2 (0.8%)	0 (0%)	2 (1.6%))	
Urological cancer	10 (4.2%)	8 (6.8%)	2 (1.6%)	
Prostate cancer	6 (2.5%)	6 (5.1 %)	0 (0%)	
Balader cancer	4 (1.7%)	2 (1.7%)	2 (1.6%)	
Stage of cancer, n (%)				0.27
Stage I or II	90 (37.2%)	48 (40.6%)	42 (33.9%)	
Stage III or IV	152 (62.8%)	70 (59.4%)	82 (66.1%)	

Table 1: Patients and tumors characteristics at the time of radiotherapy course.

"Younger old" (65-74 years) cases represented 62.7% (n=74) while "older old" (75-84 years) represented 37.3% (n=44). For the younger old, performance status was 0-1 and 2-3 in 91.9% and 8.1% respectively and the mean of CCI was 1 (max 3).

For the "older old" the mean of CCI was 4 (max 7) and they had all a performance status of 0-1. We didn't find a significant difference in term of toxicity and compliance between the two groups "younger old" and "older old" (p=0.9 and p=0.07 respectively). All treatments were

delivered using high mega voltage linear accelerators and conformal dosimetry.

Median total prescribed dose was 60.3 ± 1.5 Gy using classical fractionation (2 Gy/day) a single fraction daily for the two groups. Table 2 shows treatment related characteristics.

	Total (N=242)	Old patients (N=118)	Young patients (N=124)	p value
Irradiated sites, n (%)	-	-	-	0.4
Head and neck	56 (23.1%)	26 (22%)	30 (24.2%)	
Chest	100 (41.3%)	46 (39%)	54 (43.5%)	
Abdominopelvic sites	86 (35.5%)	46 (39%)	40 (32.2%)	
Total dose (Gray), mean ± SD	60.3 ± 15	59 ± 16	61 ± 14	0.28
Total dose, n (%)	-	-	-	0.11
≥ 70 Gray	90 (37.2%)	38 (32.2%)	52 (41.9%)	
<70 Gray	152 (62.8%)	80 (67.8%)	72 (58.1%)	
Treatment duration (days), median ± IQR	49 (30-58)	47 (34 -60)	49 (29-58)	0.16
Concomitant chemotherapy, n (%)	-	-	-	0.58
Yes	164 (67.8%)	78 (66.1%)	88 (69.4%)	
No	78 (32.2%)	40 (33.9%)	36 (30.6%)	

Table 2: Treatment related characteristics.

Therapeutic Compliance and Toxicity

For the group old patients, there was no acute toxicity in 10 patients (8.5%). 88 patients (74.5%) had grade 1–2 acute toxicity while 20 patients (17%) had grade 3-4 toxicity. In the other hand, the maximal acute toxicity for group young patients was graded 1-2 in 80 patients (64.5%), 3-4 in 26 patients (21%) and there was no acute toxicity in 18 patients (14.5%). We have detailed the toxicities observed in the two age groups in Table 3. There was no significant difference in terms of toxicities between the age groups.

Acute toxicity	All patients (n=242)	Old patients (n=118)	Young patients (n=124)
Grade 0, n (%)	28 (11.6%)	10 (8.5%)	18 (14.5%)
Grade 1 to 2, n (%)	168 (69.4%)	88 (74.5%)	80 (64.5%)
Grade ≥ 3, n (%)	46 (19%)	20 (17%)	26 (21%)

Table 3: Maximal acute toxicity scored with CTCAE v3.0.

For treatment compliance, a statistically significant difference was found between old and young patients (p=0.004). For the group old patients, the scheduled RT course was completed by 96 patients (81.3%).

Fourteen patients (11.9%) definitively stopped treatment and eight patients (6.8%) temporarily interrupted RT course. The interruption lasted from 1 to 7 days.

In the other group, RT course was completed by 116 patients (93.5%). Four patients (3.2%) definitively stopped treatment and four patients (3.2%) temporarily interrupted RT. The interruption lasted from 1 to 3 days. Table 4 shows compliance of treatment related characteristics.

Compliance of treatment	All patients (n=242)	Old patients (n=118)	Young patients (n=124)	p value
Good compliance, n (%)	212 (87.6%)	96 (81.3%)	116 (93.6%)	0.004
Moderate to poor compliance, n (%)	30 (12.4%)	22 (18.7%)	8 (6.4%)	

Table 4: Treatment compliance related characteristics.

Factors Influencing Treatment Compliance for All Patients

In univariate analysis, gender, living conditions, performance status, number of drugs, disease stage, total delivered dose, concomitant chemotherapy and toxicity grade were associated to compliance of treatment.

In multivariate analysis, factors associated with good compliance of treatment were: Age <65 years (OR=0.2, CI95% [0.05–0.79], p=0.02), male patients (OR=13, CI95% [2.6–72.1], p=0.001), not living with family (OR=17, CI95% [3–98], p<0.001), performance status ≥ 2 (OR=113, CI95% [5.9–2163], p=0.001), number of drugs ≥ 3 (OR=8, CI95% [1.14–62.3], p=0.036), radiotherapy dose ≥ 70 Gy (OR=0.13, CI95% [0.03-0.58], p=0.007), toxicity grade ≥ 3 (OR=25, CI95% [5.2–123], p<0.001). Results are displayed in Table 5.

	Univariate analysis			Multivariate analysis		
	OR	p	CI	OR	p	CI
Age (young)	0.3	0.006	0.12-0.7	0.2	0.02	0.05-0.79
Living in institution (yes)	5.2	0.014	1.3-19.9	17	0.001	3-98
Gender (male)	3.4	0.002	1.5-7.6	13	0.001	2.6-72.1
Performance status (≥ 2)	2.6	0.0001	5-1.37	113	0.001	5.9-21.63
Number of drugs (≥ 3)	2.1	0.19	0.66-7.1	8	0.03	1.14-62.3
Stage (III or IV)	2.6	0.043	1.03-6.6	4,1	0.07	0.8-20
Totale dose (≥ 70 Gy)	0.3	0.0001	0.09-0.4	0,13	0.007	0.03-0.58
Concomitant chemotherapy (yes)	2	0.13	0.8-5.2	1	0.94	0.21-5.2
Treatment duration	1	0.79	0.99-1	-	-	-
Toxicity (grade ≥ 3)	6.9	0.0001	3-15.6	25	<0.001	5.2-123

Table 5: Factors influencing treatment compliance for all patients.

Factors influencing compliance of treatment for old patients

Male gender, living in institution, good performance status, stage of cancer, radiotherapy dose and toxicity grade were associated with good compliance.

In multivariate analysis, three factors were associated with good compliance: living in institution (OR =7, CI95% [1.3–36.2], p=0.019), radiotherapy dose ≥ 70 Gy (OR=0.05, CI95% [0.006-0.65], p=0.02) and toxicity grade ≥ 3 (OR=0.05, CI95% [4.05-73.7], p<0.001). Results are displayed in Table 6.

	Old Patients					
	Univariate analysis			Multivariate analysis		
	OR	P	CI	OR	P	CI
Living in institution	5.1	0.03	1.16-22.3	7	0.019	1.3-36.2
Performance status (≥ 2)	10	0.009	1.7-61.3	12	0.14	0.44-326
Gender (male)	2	0.14	0.19-1.2	1.2	0.78	0.27-5.5
CCI	0.08	0.37	0.59-1.5	-	-	-
Number of drugs (≥ 3)	1.55	0.48	0.45-5.3	-	-	-
Stage disease (III or IV)	2	0.16	0.74-5.7	2.9	0.18	0.6-14
Concomitant chemotherapy (yes)	1.4	0.46	0.52-4	-	-	-
Total dose (≥70 Gy)	0.16	0.02	0.03-0.75	0.06	0.02	0.006-0.65
Treatment duration (days)	0.04	0.63	0.03-1.5	-	-	-
Toxicity (grade ≥ 3)	13.2	0.001	4.3-39	0.05	<0.001	4.05-73.7

Table 6: Factors influence treatment compliance for old patients.

Factors influencing treatment compliance for young patients

In univariate analysis, factors associated with good compliance included: gender, and toxicity grade. In mutltivariate analysis, only gender (OR=7.3, $CI_{95\%}$ [1.2-43.4], p=0.027) was associated with good compliance. Results are displayed in Table 7.

	Young patients					
	Univariate analysis			Multivariate analysis		
	OR	p	CI	OR	p	CI
Living place (not with family)	-	0.99	-	-	-	-
Performance status (≥ 2)	0.0001	0.99	-	-	-	-
gender (male)	9.4	0.008	1.8-49.38	7.3	0.027	1.2-43.4
Number of drugs (≥3)	-	0.999	-	-	-	-
Stage (III or IV)	-	0.99	-	-	-	-
Concomitant chemotherapy (yes)	-	0.99	-	-	-	-
Total dose (≥ 70 Gy)	0.44	0.32	0.08-2.2	-	-	
Treatment duration (days)	1	0.84	0.99-1	-	-	-
Toxicity (grade ≥ 3)	4.2	0.05	0.99-18.4	1.9	0.42	0.38-9.56

Table 7: Factors influencing treatment compliance for young patients.

Discussion

This is a prospective case-control study of patients treated with radiotherapy in a curative intent. We aimed to evaluate treatment compliance in different age groups of patients undergoing radiotherapy and bring out to light factors influencing treatment compliance.

Both groups, old versus young patients had the same toxicity profile unlike what was expected. Nevertheless, old patients had an increased risk to interrupt or stop treatment and that risk was associated with their residence place, gender, delivered radiotherapy dose and the toxicity grade.

A study by Wasil and colleagues has examined the issue of RT in 183 patients 80 years and older diagnosed with cancer. They found that 77% of patients were able to complete the prescribed therapy [5]. The percentage of patients who completed scheduled RT in our series is higher. This may be explained by the fact that our patients are younger (age ≥ 65). Another study by Firvida and all confirms that advanced age is associated with poor treatment compliance. It also stated that performance status is a useful clinical index correlated with good compliance [19].

Living place was not significantly associated to treatment compliance in any other publication. In our study, patients living in institution had a decreased risk to interrupt or to stop treatment, which may be explained by the presence of a house caregiver. Clinicians need to provide more attention and proper counseling to these patients to maintain an effective care.

Radiation associated toxicities are known to be dose dependent and strongly correlated to irradiated normal tissue volume as well as the physiologic function of the exposed normal tissue. However, since toxicities are not consistently associated with age [20], published toxicity risks are not stratified by age. In our study we didn't find any difference of radiation associated toxicities between the two groups.

Actually, the use of advanced RT techniques like stereotactic body , volumetric RT and image-guided RT had allowed the delivery of high doses of radiation to small target volumes while limiting the risk of radiation-induced damage to normal surrounding tissues and organs at risk [6]. Concomitant chemotherapy brings higher risk of acute toxicity than single modality therapy [21]. The NCCN guidelines recommends to prescribe chemotherapy, when indicated, to elderly patients with good performance status because they can tolerate commonly used chemotherapy drugs as well as younger patients do, especially when they receive adequate supportive care [22]. Similarly, in our study, the combination of chemotherapy and radiotherapy in the elderly does not interfere with treatment compliance.

This study has several strengths and some limitations. Our study is about relatively large sample size, and it is one of the few available studies that compare treatment compliance and radiation associated toxicities between old and young patients undergoing RT with curative intent based on standardized guidelines for the assessment of toxicities.

The major limitations is that our patients didn't receive an oncogeriatric consulting before treatment start and we didn't assure a follow up after the end of RT to evaluate late toxicities.

Conclusion

Age alone should not be considered independently. Older patients, when selected carefully, appear to tolerate well RT. Living conditions as well as the prescribed dose should be assessed and taken in consideration before treatment planning. But we still need prospective randomized controlled clinical trials of cancer treatments in old age to assure the best management for this specific patient group.

Ethics Approval and Consent to Participate

Informed consent (verbal) was obtained from all participants. This study was submitted to and approved by research and ethics committee of National Institute of Oncology.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

Special thanks are due to the Faculty of Medicine and Pharmacy of Rabat; the source(s) of funding for all authors.

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