

**ORIGINAL STUDY**

**THE INFLUENCE OF OLD AGE UPON THERAPEUTIC DECISIONS  
AND RESULTS IN PELVIC MALIGNANCIES RADIOTHERAPY**

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**ABSTRACT**

*The management of oncologic treatment in geriatric context is complex due to the toxicity of loco-regional treatment and co-existing illness; the radiotherapist must, in many cases, to adapt the treatment schemas in order to decrease the potential adverse effects in these frail patients. This retrospective study analyses 92 patients aged  $\geq 80$  years (mean age 82.71 years, range 80-95 years) who performed external beam radiotherapy for pelvic malignancies in Radiotherapy Department, „Sf.Ap.Andrei” Emergency Clinical Hospital, Galati, between 01.01.2007 and 31.12.2011. Predominated subgroup of age was 80-85 years (80.43% of cases); 54.35% of patients were men and 45.65% women, most of them from urban environment (63.04% of cases). Advanced local disease presented 90.21% of cases. Performance status 0-1 and respective 2-3-4 presented 35.78% and respective 64.31% of patients. The most frequent tumor sites were rectum, prostate, cervix, and respective endometrium in 30.43%, 27.17%, 16.3% and respective 13.04% of cases. No concomitant treatments, radio-chemotherapy, were performed. Considering the impact upon the patient's performance status, the co-morbid diseases were also analyzed. The mean follow-up was 20.79 months (range 2-58 months). Curative and palliative treatment had been administrated for 55.43% and respective 44.57% of cases, with standard fractionation (66.30%) and with hypofractionation schedules (33.7%). A percent of 13.04% of cases interrupted their treatment at smaller radiation doses respect of intended dose due to poor general status, progression of disease and patient's refusal. The tolerance of treatment was good. The most frequent acute reactions recorded were gastrointestinal (43.48% of cases), urinary (11.96%); 7 patients (7.61%) presented leukopenia grade 1 and 2; anemia, which had multiple etiologies, was recorded at 20 patients (21.74%). Of all patients, only for 5 patients (5.43%), the recorded toxicities required the treatment interruption for 5-7 days. Global survival at 5 years was 71%. The patients with poor performance status had a significant smaller survival respect of good performance status patients, 60% versus 83%,  $p=0.01$ . For patients with stage III and IV of disease, the 5-years survival was 73% and 60% respective,  $p=0.03$ . The treatment must be adapted to age and the results must be interpreted with precaution suggesting that the therapeutic strategies that generate strong adverse effects must be adapted and evaluated in geriatric context.*

**KEYWORDS:** radiotherapy, geriatric oncology and elderly patient.

**1. Introduction**

The management of oncological treatment in a

geriatric context is complex, due to the high toxicity of loco-regional treatments and, also, due the co-morbidities; most of the times, the physicians have to

adapt the treatment schedule to decrease potential adverse effects in these frail patients. Never the less, there are few literature data regarding risk factors, treatment schedules and results of elderly patients [1].

In the last years life expectancy is increasing; men living to 80-85 years can expect to live approximately 5-7 more years, while for women the life expectancy can be even longer, with 1–2 years of longevity in addition to those of men's [2].

Elderly patients may be treated less aggressively than younger patients with the aim of preserving quality of life and decreasing of toxicities, taking into account that their radiotherapy tolerance can be reduced and their life expectancy is short. Even if 50% of all cases occurring in patients aged 70 or over, data on tolerance of treatment are limited [2]. The elderly patients present a considerable degree of biological heterogeneity; co-morbidities together with varying physiological reserves signify the following aspect: the key factor in treatment tolerance appreciation is not only the chronological age, but also the performance status [2].

We can talk about an adapted treatment, conforming to the institution guidelines, which defined the following situations of treatment adaptation:

- patients with resectable tumors who refused the surgical treatment and performed radical radiotherapy
- the cases with adjuvant radiotherapy indication not-performed, but in stead performed surgical treatment
- the cases without lymph node radiotherapy or without lymph node dissection when these indications existed
- unconventional fractionation
- lower radiation dose respect of planned dose.

## 2. Material and Methods

We have studied a lot of 92 pelvic

malignancies patients over 80 years of age, who performed external beam radiotherapy in Radiotherapy Department of „Sf.Ap.Andrei” Emergency Clinical Hospital, Galati. The mean age was 82.71 years (range 80-95 years). A percent of 80.43% of studied patients was in 80-85 years group of age (figure 1).

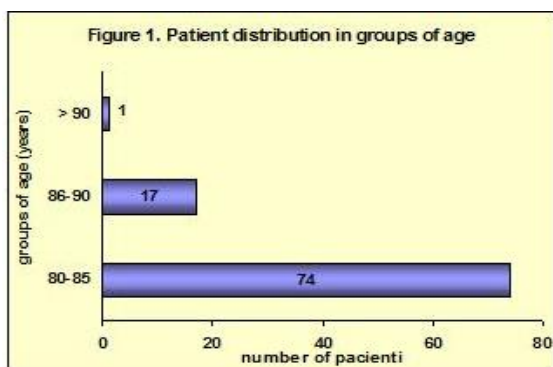
In this lot 54.35% were men and 45.65% were women. The urban cases predominated in our lot, being 63.04% of patients. The great majority presented advanced local disease, stages III and IV; 9.78% of cases had stage II of disease (table I a).

The most frequent histological type was adenocarcinoma in 64.13% of cases, followed by squamous cell carcinoma in 32.16% of cases and only 3 cases with transitional carcinoma (table I a)

Regarding performance status (PS), 64.13% of cases presented low performance status of 2,3 or 4, and 35.78% presented PS of 0 or 1 (table Ia).

**Table I a.** *Clinical characteristics*

Parameters	No. patients (%) N=92
<b>Mean age (years)</b>	<b>82.71 (range 80-95)</b>
<b>Group of age (years)</b>	
80-85	74 (80.43)
86-90	17 (18.48)
> 90	1 (1.09)
<b>Environment</b>	
Urban	58 (63.04)
Rural	34 (36.96)
<b>A. Sex</b>	
Male	50 (54.35)
Female	42 (45.65)
<b>B. Disease stage</b>	
I	0
II	9 (9.78)
III	51 (55.43)
IV	32 (34.78)
<b>C. Histology</b>	
Adenocarcinoma	59 (64.13)
Squamous cell carcinoma	30 (32.61)
Transitional carcinoma	3 (3.26)
<b>D. Tumor differentiation</b>	21 (22.83)
G1	41 (44.57)
G2	24 (26.09)
G3	6 (6.52)
G4	
<b>Performance status</b>	33 (35.87)
0-1	59 (64.13)
2-3-4	

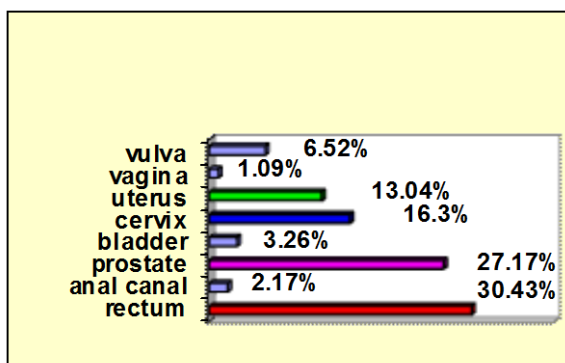


**Figure 1.** Patient distribution in groups of age

The most frequent neoplastic site were rectum and prostate (30.43% and 27.17%, respective), followed by cervix and uterus (16.3% and 13.04%, respective). We have found only one case of vagina tumor, representing 1.09% of total cases (table II.b and figure 2)

**Table I. b Clinical characteristics**

E. Parameters	No. patients (%) N=92
<b>Neoplastic site</b>	
Rectum	28 (30.43)
Anal canal	2 (2.17)
Prostate	25 (27.17)
Bladder	3 (3.26)
Cervix	15 (16.3)
Endometrium	12 (13.04)
Vagina	1 (1.09)
Vulva	6 (6.52)



**Figure 2.** The patient's distribution of pelvic malignancy site

We followed also the co-morbidities knowing the impact upon patient's performance status. We

found multiple co-morbidities on the studied patients and these are showed in table 2; the most frequent co-morbidities were: hemorrhoid disease, (51.09%), high blood pressure (19.57%), diabetes mellitus type II (7.61%), coronary disease (7.61%), atrial fibrillation (5.43%), hearing impaired (6.25%), previous stroke (4.35%), and chronic kidney failure (6.25%). A percent of 58% of patients presented, associated with malignant disease, two or more co-morbidities, 29% of patients presented only one co-morbid illness and 13% did not presented any co-morbid illness.

**Table II. Comorbidities**

Comorbidities	No. patients (%) N=92
High blood pressure	18 (19.57)
Diabetes mellitus type II	11 (7.61)
Coronary disease	7(7.61)
Heart failure	3 (3.26)
Atrial fibrillation	5 (5.43)
Previous stroke	4 (4.35)
1. Hearing impaired	6 (6.52)
2. Pulmonary emphysema	4 (4.35)
Chronic kidney failure	6 (6.52)
Obesity	3 (3.26)
Chronic hepatitis	2 (2.17)
Alzheimer disease	2 (2.17)
Haemorrhoid disease	47 (51.09)

We did not perform concomitant chemo-radiotherapy because of age and co-morbidities criteria.

The therapeutically characteristics of studied patients are showed in table III. Local curative treatment performed 51 patients (55.43% of cases). Palliative treatment performed 41 patients (44.57% of patients) (figure 3).

Palliative treatment was performed tanking into account the following criteria:

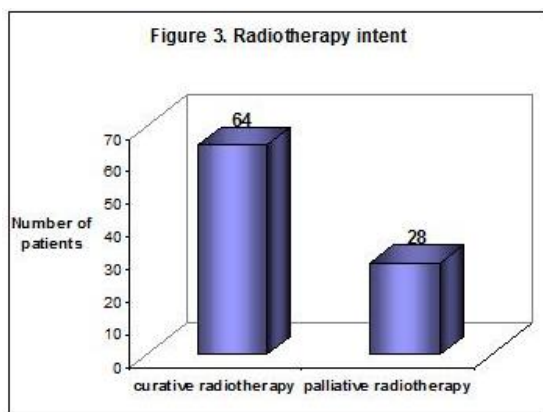
- patients with loco-regional advanced disease, tumor stage III and IV,
- multiple co-morbidities,
- performance status  $\geq 3$ .

The radiotherapy was effectuated at the radiotherapy units Rokus M 40 and Theratron Elite

100, in „box” technique for rectal, prostate, cervix and endometrium cancer patients.

**Table III. Therapeutically characteristics**

F. Parameters	No. patient (%) N=92
<b>Radiotherapy type</b>	
Curative	51 (55.43)
Palliative	41 (44.57)
<b>Fractionation</b>	
Conventional	61 (66.30)
Hypofractionation	31 (33.69)
<b>Treatment complete</b>	80 (86.96)
<b>Treatment interrupt</b>	12 (13.04)



**Figure 3. Radiotherapy intent**

The radiotherapy with curative intent is feasible for good performance status patients and for whom the neoplastic disease cannot be controlled by surgery.

Endometrium cancer patients from our lot did not performed surgery because of non-compliant behavior and because of anesthesia contraindications.

There are more treatment schemas administrated during curative treatment for prostate, bladder, cervix and endometrium cancer, respective: TD (total dose) =66Gy/33 fractions/6-7 weeks, dose/fraction = 180–200cGy, TD = 50Gy/25 fractions /5 weeks, dose/fraction = 200cGy and TD = 40Gy/20 fractions / 4 weeks, dose/fraction = 200cGy.

*Statistical analysis*

Survival curves were performed using Kaplan–Meier method and differences between them were evaluated using Log-rank test. The significant test of

differences’ proportion was evaluated using Fisher test (2-tailed) for categorical variable and Student t test for continuous variables. All statistical tests were 2-sided, and p values <0.05 indicated statistical significance. Analyses were performed using XLSTAT statistical software.

**3. Results**

Median follow-up was 20.79 months (range 2-58 months). We did not recorded patients who died during radiotherapy. Four patients were lost from follow-up and they were excluded from survival analysis.

A number of 12 patients interrupted their treatment due to disease evolution (3 patients), patient’s refusal to continue the treatment (4 patients) and for 5 patients the treatment was interrupted due to radiotherapy’s acute reactions, thus: because of grade 2 enteritis, two patients interrupted treatment for 5-7 days; the radiotherapy was continued after the symptomatically treatment was performed; another 2 patients interrupted radiotherapy because of rectal bleeding and one patient interrupted because of leukopenia; for leukopenia the patients received corticosteroid treatment.

*Acute reactions*

Grade 1 and 2 acute reactions post radiotherapy were skin, digestive, urinary and hematological reactions in 12%, 43.48%, 11.96% and respective 29.34% of cases (table IV).

Skin reactions were recorded in 12% of cases, as grade 1 and 2 acute radiation erythema on irradiated skin at the end of the treatment and did not require the interruption of radiotherapy.

From hematological point of view, 20 patients presented grade 1 anaemia and 7 patients presented grade 1 and 2 leukopenia, corrected with cortisone treatment.

Gastrointestinal reactions were recorded at 40

patients (43.48% of cases); 28.26% of cases had grade 1 and 2 diarrhea, and 15.22% of patients had radiation induced rectal toxicity.

Urinary reactions – radiation cystitis manifested at 11.96% of patients. The urinary reactions were remitted with anti-inflammatory and anti-spastic treatment.

**Table IV.** Radiotherapy acute reactions

Parameters	No. patients (%) N=92
<b>Skin reactions</b>	
Radiation erythema	11 (12)
<b>Hematological reactions</b>	
Grade 1 and 2 leucopenia	7 (7.61)
Anaemia	20 (21.74)
<b>Gastrointestinal reactions</b>	
Grade 1 and 2 diarrhea	26 (28.26)
Rectal toxicity	14 (15.22)
<b>Urinary reactions</b>	
Radiation cystitis	11 (11.96)

*Survival*

Survival rates were analyzed from the date of treatment beginning to the date of death or most recent follow-up date.

From therapeutically intent point of view, curative radiotherapy patients had a disease specific survival (DSS) of 86% at 5 years, significant greater than palliative radiotherapy patients with DSS of 57%,  $p=0.04$  (figure 4).

Regarding performance status, patients who presented PS = 2, 3 or 4 had a survival rate statistical significant lower (60%),  $p=0.01$ , than patients with PS = 0 or 1 (83%) (figure 5).

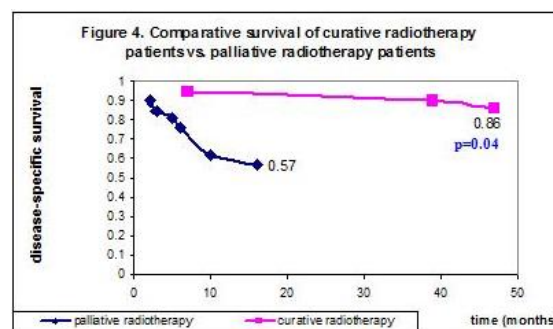
The five years survival rates function of disease stage evidenced a statistic significant difference between the survival rate of patients with stage III of disease, which is 73% and the survival rate of patients with stage IV of disease, which is 60%,  $p=0.03$ .

Comparing five years rate survival of stage II patients (89%) with five years rate survival of stage III patients, 73%, we found a strong statistical difference,  $p<0.01$  (Fisher test) (figure 6).

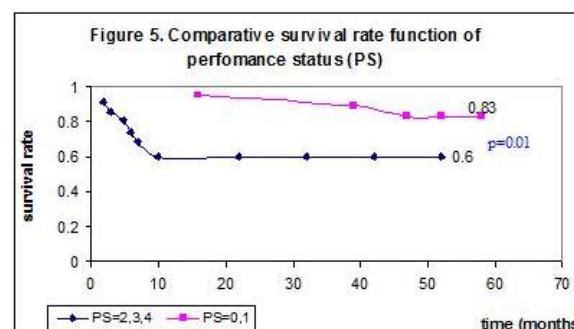
Knowing that the great majority of patient with stage II of disease had cervix carcinoma and making the correlation between survival rate function of disease stage and survival rate function of primary malignant site, we have observed a good correlation between these two parameters – the best survival rate have been recorded for cervix carcinoma patients; at five years, the survival rate was 86% (figure 7).

Correlation test 1WayAnova ( $p=0.02$ ) and correlation coefficient Pearson, confirm this affirmation.

Also, the correlation coefficient Pearson evidence that does not exist a correlation between age and survival rate, neither between age and the follow-up period. But does exist correlation between survival rate and performance status, meaning that a PS = 0 or 1 is correlated with a greater five years survival rate.



**Figure 4.** Comparativ survival of curative radiotherapy patients vs. palliative radiotherapy patients



**Figure 5.** Comparativ survival rate function of performance status

Making the comparison between survival rate of studied patients function of tumor’s site, we have

observed that the smaller survival was recorded for rectal cancer patients being 46%, and for prostate adenocarcinoma patients, the five years survival rate was 82%,  $p=0.0003$ .

The best survival rate was recorded for cervix carcinoma patients, 86%, with statistical significant differences respect of endometrial cancer patient survival rate, 75% ( $p=0.01$ ).

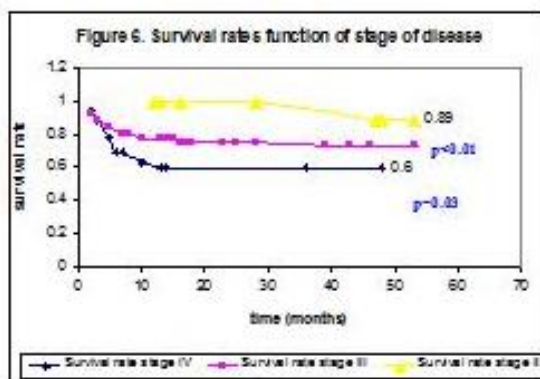


Figure 6. Survival rates function of stage of disease

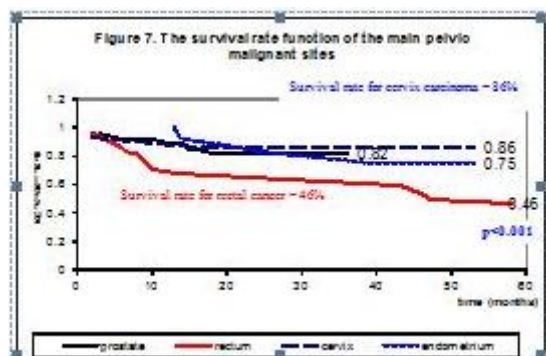


Figure 7. The survival rate function of the main pelvic malignant sites

Even if actual therapeutically protocols indicate, for endometrium neoplasm, the surgery performing prior radiotherapy, our patients with endometrium cancer, did not performed surgery due to noncompliance behavior or due to anesthesia contraindications.

The five years overall survival (OS) for our patients was 71%. OS is defined as the interval between diagnosis and the date of death or of last follow-up (figure 8). The univariate analysis

evidenced that performance status, the age at the date of treatment's initiation, the site of malignancy and stage of disease were associated with a better five years survival rate.

The multivariate prognostic analysis indicated that only performance status was an independent prognostic factor.

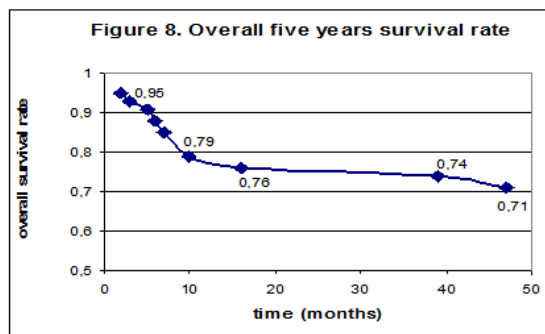


Figure 8. Overall five years survival rate

#### 4. Discussions

The treatment of pelvic cancers at elderly patients is complex in geriatric context, because of treatment high toxicities and co-morbid illnesses. Satisfactory skin and hematological tolerance permitted the radiotherapy performing, for the great majority of studied patients, until the prescribed total doses.

In our study 86.96% of cases finished their treatment at the prescribed total doses and 13.04% of patients did interrupt the treatment at smaller doses respect those prescribed, because of general state degradation, disease progression and patient's refusal.

During pelvic radiotherapy the gastrointestinal adverse reactions (grade 1 and 2 radiation diarrhea and radiation rectal toxicity) are almost inevitable. These acute reactions can produce, when are severe, an important discomfort and/or important changes in patient's feeding which can have a disastrous effect, especially upon elderly patients. [3].

Predictive factor identification for radio-

induced toxicity represents a complex process: radiotherapy late effects are related with dosimetric factors, clinical risk factors and, also, with the genetic profile of patient.

In a systematic review, Fiorino et al. [4] found that patients with diabetes mellitus and patients with haemorrhoids presented a higher risk of acute reactions development; diabetes mellitus was strongly associated with acute severe diarrhoea, and the haemorrhoids' presence was predictive factor for acute gastrointestinal toxicity, rectal bleeding and tenesmus [5].

Some authors found as risk factors for rectal bleeding development, which are not related with dose-volume parameters, for example, the abdominal or pelvic surgery were found to be associated with a high risk of rectal bleeding [6,7].

For low performance status patients should be recommended palliative external beam radiotherapy. Hypofractionation schedules are not optimal from radiobiological point of view because of reducing of radiation dose intensity and promoting the tumor repopulation, but on the other hand, the dose per fraction increasing lead to the increasing of toxicity.

Palliative radiotherapy demonstrated their efficiency, knowing that there are many studies evidencing that in advanced incurable stages, the aggressive multimodal curative treatments did not prove clearly a benefit.

## 5. Conclusions

This retrospective analysis of the patients over 80 years old, with malignant pelvic disease, treated in our department, demonstrated that for a selected group of patients, the treatment was well tolerated with minimal toxicities.

There are a great number of co-morbid illnesses associated with neoplastic disease, which can

complicate the elderly patient radiotherapy performing.

The chronological age is not a real indicative for the frailty of these patients, does not reflect the biological age and cannot be used as selection criteria of patients or for therapeutical strategy.

The advanced treatment techniques determined the increasing of longevity and of number of patients who performed radiotherapy.

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