

## ORIGINAL ARTICLE

# Radical therapy for muscle-infiltrating bladder cancer (cystectomy or radiotherapy): does age affect the final therapeutic benefit for the patient?

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## Summary

**Purpose:** To evaluate the therapeutic outcome of radical cystectomy and radical radiotherapy in patients with T2N0M0 clinical stage bladder cancer in relation to their age.

**Patients and methods:** Between 1995-2006, 119 patients with clinical stage T2N0M0 bladder cancer were treated with radical radiotherapy (group A) and were divided in 2 subgroups: >70 years old (A1) and ≤70 years old (A2). Between 1998-2006, 26 patients with the same clinical stage were treated with radical cystectomy (group B) (>70 years old/B1 subgroup and ≤70 years old/B2 subgroup). The following parameters were evaluated in both groups and subgroups: therapeutic outcome (overall survival/OS, local control, development of metastases) and tolerance (side effects and complications of each method). Kaplan-Meier method and log-rank test were used for statistical analyses.

**Results:** All group B patients tolerated their treatment

very well, without interruptions. The 3-year OS of groups A and B was 39 and 69%, respectively ( $p=0.032$ ). The 3-year OS of subgroups A1 and A2 was 37.3 and 43.3%, respectively ( $p=0.085$ ). In the cystectomy group B, 3-year OS of the subgroups was the same (B1: 68.6% and B2: 69.3%;  $p=0.10$ ). Local control rate for the subgroups A1, A2, B1, B2 was 43, 40, 90 and 84%, respectively. Distant metastatic rate was 14.1, 20, 7.6 and 7.4% for subgroups A1, A2, B1, B2, respectively.

**Conclusion:** The results of both therapeutic methods in both age groups seem satisfactory. Very good tolerance was also observed. It seems that if a patient is not completely suitable for radical cystectomy or radical radiotherapy age should not be considered as an exclusion factor.

**Key words:** age, bladder cancer, cystectomy, muscle-infiltrating, radiotherapy, survival

## Introduction

Bladder cancer incidence ranks 7th and is responsible for the 3% of deaths from malignancies in humans [1].

Important risk factors, as defined by the European Association of Urology guidelines of 2007 [2] are:

1. Smoking: b-naphthylamines and nitrosamines are implicated. The most important risk factor, particularly if combined with professional exposure.
2. Professional exposure to chemicals: aromatic amines (tires factories, leather or textile factories, paint and fuel factories, printerries, hairdressers, etc.).
3. Race: white people of America have a 2-fold higher risk than black people.
4. Age: only 1% of bladder cancer patients are ≤40 years old.
5. Gender: in men there is a 4-fold higher frequency than in women (higher professional exposure to carcinogens or smoking frequency).
6. Chronic cystitis, chronic catheterization of the bladder.
7. Schistosoma hematobium.
8. History of prior superficial bladder cancer.
9. Congenital anomalies of the area.
10. Fatty food, lack of vitamin A, chlorinated water.

11. Drugs: cyclophosphamide, phenacetin.
12. Alcohol.
13. Genetic predisposition.

The most recent classification of bladder cancer is that of WHO 2004 in accordance with TNM 2002. The present study included patients with muscle-infiltrating bladder cancer of clinical stage T2N0M0.

The therapeutic options for these patients are radical cystectomy and/or radical radiotherapy.

Radical cystectomy is the gold standard for T2N0M0 patients in most of the countries (Europe, America). In some countries (including the U.K.) urologists favor the preservation of the organ (radiotherapy) and leave cystectomy behind as a salvage therapy only [3-6]. Patients are selected according to age, general health, tumor stage, and patients' wish. Over 60% of the patients are not suitable for radical cystectomy. Intersurgical mortality varies from 1.2% [7] to 3.7% [8] depending on the study. 5-year survival is 40-60% [9]. p53 does not seem to be predictive of overall survival in muscle-infiltrating bladder cancer [10-13], and neoadjuvant chemoradiotherapy does not offer better survival [14-18].

Radical radiotherapy can be proposed by the doctor to the patient as a primary treatment option but it can also be the only option in patients unsuitable for radical cystectomy: stage  $\geq$  T3b, bad general health, patient's wish. In external radiotherapy the field includes the bladder with a safety margin of 1.5-2 cm due to the organ movement. Total dose is up to 60-66 Gy, daily dose is 1.8-2.0 Gy and the total therapy period does not exceed 6-7 weeks. 5-year survival is 40-60%, with cancer specific survival  $<$  38%. Local recurrence happens in 30% of the cases.

In this retrospective study we surveyed the therapeutic effect and the tolerance of both of these treatment methods in patients  $>$  70 years of age suffering from clinical stage T2N0M0 bladder cancer. These results were compared with a second group of patients  $<$  70 years old in order to determine if age affects the final therapeutic result of each method (assuming that all other variables were about the same).

## Patients and methods

Between 1995-2006, 119 patients were treated with radical radiotherapy (group A) at the Radiotherapy Department of University Hospital of Ioannina (UHI) and were subdivided in 2 subgroups: subgroup A1:  $>$ 70 years old (n=80) and subgroup A2:  $\leq$ 70 years old (n=39). Clinical stage was T2N0M0 [19]. Considering the tumor histological grade, 13 patients had grade II cancer, 88 grade III, and 18 grade IV. In one patient

there was no histological report and the grade of one patient could not be assessed.

Between 1998-2006, 26 patients also with T2N0M0 clinical stage were treated with radical cystectomy at the Urology Department of the General Hospital of Ioannina (GHI) (group B). Histological grade was II in 6 patients, III in 16, IV in 3 and undetermined in 1 patient. Sixteen patients were aged  $>$ 70 years (B1 subgroup) and  $10 \leq 70$  years (B2 subgroup). Clinical staging was carried out by initial transurethral biopsy, bimanual examination of the bladder under sedation, i.v. pyelography, CT of the thorax and abdomen, and whole-body bone scan.

All group A patients were treated with linear accelerator (6 MV) using the Box technique. The total dose delivered was 64 Gy (range 60-66) in 32-36 fractions. 44 Gy were given to the pelvis and 20 Gy as a boost. The daily dose was 1.8-2.0 Gy.

Twenty-two (85%) patients were operated with the Bricker procedure using ileal conduit urinary diversion and 4 (15%) with orthotopic neobladder pouch using parts of ileum or the sigmoid [20-22].

The parameters studied were: overall survival of groups A and B; overall survival of subgroups A1, A2 and B1, B2; local control rate; distant metastatic rate; side effects and complications of the 2 treatment modalities in each age group.

## Statistical methods

The SPSS version 14.0 statistical package was used for statistical analyses. Descriptive statistics were reported as percentages and medians. OS curves were constructed using the Kaplan-Meier method. Log-rank test was used to compare survival curves. OS was determined from the day of diagnosis until death.

## Results

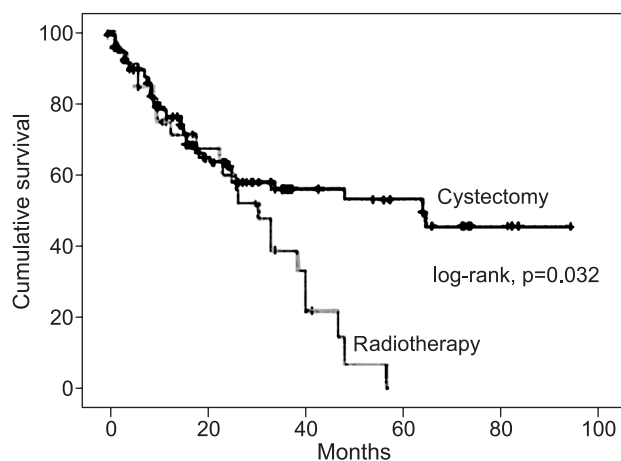
### Survival

The average follow-up period was 38.4 months for group A (range 5-125) and 37.2 months for group B (range 8-89).

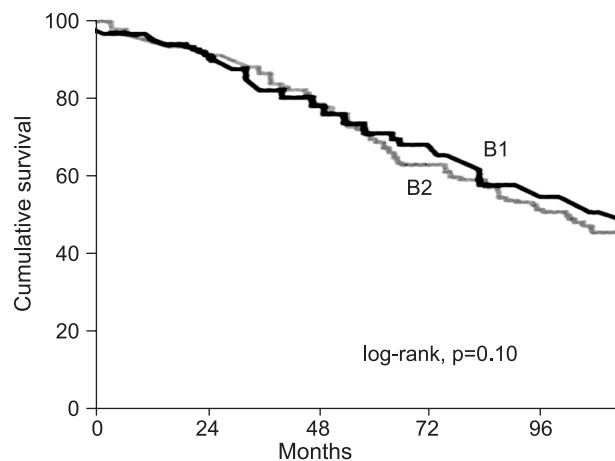
OS at 3 years (any age) of radical cystectomy and radical radiotherapy groups was 69% and 39%, respectively (p=0.032; Figure 1).

OS at 3 years between subgroups A1 ( $>$  70 years) and A2 ( $\leq$  70 years) was 37.3 and 43.3%, respectively (p=0.85; Figure 2).

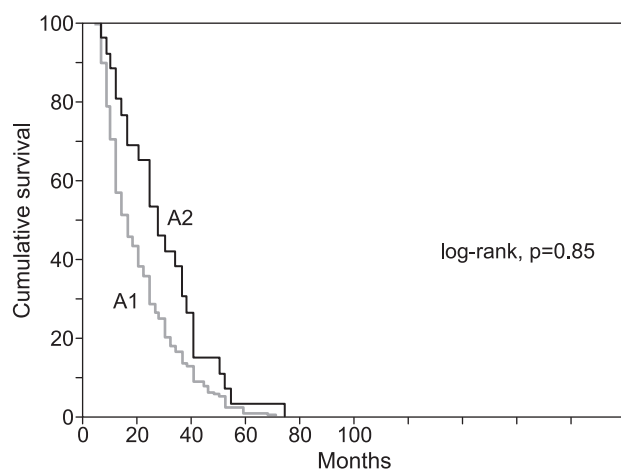
In the cystectomy group no statistically significant difference was observed between subgroups B1



**Figure 1.** Kaplan-Meier overall survival of patients treated with radical cystectomy and radical radiotherapy.



**Figure 3.** Kaplan-Meier overall survival between B1 (>70 years old) and B2 (≤70 years old) subgroups of cystectomy.



**Figure 2.** Kaplan-Meier overall survival between A1 (>70 years old) and A2 (≤70 years old) subgroups of radiotherapy.

and B2 concerning OS at 5 years (B1: 68.6% and B2: 69.3%, respectively;  $p=0.10$ ; Figure 3).

Local disease control rate for the groups A1, A2, B1, B2 was 43, 40, 90, and 84%, respectively. Local control was slightly better in patients aged > 70 but without statistical significance.

During follow-up distant metastases developed in 14.1, 20, 7.6, and 7.4% for subgroups A1, A2, B1, B2 patients, respectively. Statistical significance ( $p=0.023$ ) was seen between subgroups A1 and A2 but not between subgroups B1 and B2 ( $p=0.14$ ).

In the radiotherapy group A of patients, where the primary tumor was not removed, the younger group of patients (A2) had a statistically significant higher percentage of distant metastases at 3 years ( $p=0.042$ ).

### Complications and side effects

The majority of group A patients developed minor side effects (cystitis, diarrhea) according to WHO toxicity criteria, which were all treated symptomatically (Table 1). No patient interrupted treatment because of side effects.

In group B the incidence of the postoperative complications (acute or late) was 46.1% (12/26 patients). Purulence of the surgical trauma was observed in 19.23% (5/26 patients), symphytic bowel obstruction in 7.69% (2/26 patients), pulmonary embolism in 7.69% (2/26 patients), urinary incontinence in 3.85% (1/26 patients), and stenosis of the ureteroileostomy in 3.85% (1/26 patients). One patient died the in 2nd postoperative day due to massive pulmonary embolism (Table 2).

### Discussion

The age of patients treated for bladder carcinoma is an independent prognostic factor for survival, according to the international literature [23-28]. Radical cystectomy is the gold standard for the treatment of muscle-infiltrating bladder cancer and the survival offered by this treatment modality is incomparably better than the one achieved by radical radiotherapy [29-32].

According to our results, external radiotherapy in muscle-infiltrating bladder cancer is an acceptable therapeutic method with good tolerance among aged patients [33].

Our study showed that OS and local control rate after radical cystectomy were similar in both age groups. Local control was slightly better in patients

**Table 1.** Toxicity of all patients (n=119) treated with radical radiotherapy (subgroups A1 and A2)

<i>Toxicity</i>	<i>Grade 1 n (%)</i>	<i>Grade 2 n (%)</i>	<i>Grade 3 n (%)</i>
<b>Gastro-intestinal and urological</b>			
nausea-vomiting (A1-A2)	21 (18) (13/80-8/39)	10 (8.9) (7/80-3/39)	0
cystitis (A1-A2)	42 (35) (31/80-11/39)	12 (11) (8/80-4/39)	0
diarrhea (A1-A2)	18 (15) (14/80-4/39)	10 (8.9) (8/80-2/39)	8 (6.6) (6/80-2/39)
<b>Hematological</b>			
leukopenia (A1-A2)	12 (11) (10/80-2/39)	44 (37) (32/80-12/39)	8 (6.6) (6/80-2/39)
anemia (A1-A2)	40 (31) (35/80-5/39)	12 (11) (9/80-3/39)	3 (2.2) (3/80-0/39)
thrombocytopenia (A1-A2)	15 (13) (11/80-4/39)	5 (4.5) (4/80-1/39)	

**Table 2.** Incidence of postoperative complications in group B (radical cystectomy)

<i>Type of complication</i>	<i>Patients, n</i>	<i>%</i>
Purulence of the surgical trauma	5/26	19.23
Symphytic bowel obstruction	2/26	7.69
Pulmonary embolism	2/26	7.69
Urinary incontinence	1/26	3.85
Stenosis of the ureteroileostomy	1/26	3.85
Lethal massive pulmonary embolism	1/26	3.85
Total	12/26	46.1

aged > 70 years. This can be explained if we consider the aggressiveness of cancer, especially in younger patients. On the other hand, the incidence of postoperative complications in the aged group of patients was not significantly higher compared to what appears in the relevant literature [34-37].

It the radiotherapy group of patients the distant metastatic rate was statistically significantly higher among younger patients (A2), possibly due to the biological behavior of cancer concerning age. In both A2 and B2 subgroups of patients, local recurrence rate was slightly increased in the 3-year period, when compared with the aged patients (A1, B1).

Finally it seems that both treatment methods can be applied to the older patients with very good results.

In conclusion, the 70-year-old limit for radical cystectomy as adopted in most study series in many institutions seems to be not so unconditional as consid-

ered in the first place [24,25,38,39]. Many factors can overrule this limit: general patient condition, the surgical method used and of course the current prolonged life expectancy.

Improved methodology and accuracy concerning 3D techniques and high resolution CT scans contributing to much more accurate imaging and target calculating techniques, in combination with newer socio-epidemiological data have also transposed the age limit upwards for radical radiotherapy also [40-42]. Selection of the patient suitable for therapy has become more complicated and challenging because results are so little affected by age.

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