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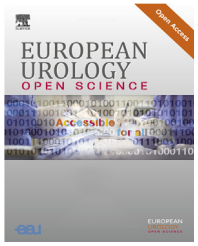

European Association of Urology

Urothelial Cancer

Sarcopenia Predicts Disease Progression in Patients with T1 High-grade Non–muscle-invasive Bladder Cancer Treated with Adjuvant Intravesical Bacillus Calmette-Guérin: Implications for Decision-making?

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Abstract

Background: Skeletal muscle loss (sarcopenia) has been linked to cancer cachexia and can predict survival in several tumors, including advanced genitourinary malignancies.
Objective: To investigate the predictive and prognostic role of sarcopenia in patients with T1 high grade (HG) non-muscle invasive bladder cancer (NMIBC) treated with adjuvant intravesical Bacillus Calmette-Guerin (BCG).
Design, setting, and participants: Oncological outcomes were evaluated for 185 patients with T1 HG NMIBC treated with BCG at two European referral centers. Sarcopenia, identified from computed tomography scans performed within 2 mo after surgery, was defined as a skeletal muscle index of <39 cm^2/m^2 for women and <55 cm^2/m^2 for men.
Outcome measurements and statistical analysis: The main endpoint was the association between sarcopenia and disease recurrence and progression. Kaplan-Meier curves and multivariable Cox models were built, and the clinical value of any association was assessed using Harrell's C index and decision curve analysis (DCA).
Results and limitations: Sarcopenia was present in 130 patients (70%). On multivariable Cox regression analyses that accounted for the effect of standard

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clinicopathological prognosticators, sarcopenia was independently associated with disease progression (hazard ratio 3.41; $p = 0.02$). Addition of sarcopenia to a standard model for prediction of disease progression improved the discrimination of the model from 62% to 70%. DCA revealed superior net benefits for the proposed model in comparison to the strategies of treating all or no patients with radical cystectomy, and in comparison to the existing predictive model. Limitations are inherent to the retrospective design.

Conclusions: We demonstrated the prognostic role of sarcopenia in T1 HG NMIBC. Pending external validation, this tool could be easily incorporated into existing nomograms for prediction of disease progression to improve clinical decision-making and patient counseling.

Patient summary: We looked at the role of loss of skeletal muscle (sarcopenia) as a factor in predicting prognosis for stage T1 high-grade non–muscle-invasive bladder cancer. We found that sarcopenia is a ready-to-use, cost-free marker that could be used to guide treatment and follow-up in this disease, although the results need to be confirmed in other studies.

1. Introduction

Optimal management of T1 high-grade (HG) non–muscle-invasive bladder cancer (NMIBC) remains a challenge. Standard treatment includes a second-look resection (repeat transurethral resection of the bladder [TURB]) followed by adjuvant intravesical bacillus Calmette-Guérin (BCG) for up to 3 yr [1]. Despite adequate treatment, approximately 35–45% of patients will develop HG recurrence during BCG therapy (BCG-unresponsive) and 10–15% will experience progression to muscle-invasive disease [2]. Identification of those who will not respond to BCG is of fundamental importance in selecting patients for early radical cystectomy (RC) or novel clinical trials of intensified bladder-sparing strategies, thereby improving oncological outcomes with a better balance between undertreatment and overtreatment. Moreover, the ongoing BCG shortage supports the need for early identification of patients who are unlikely to respond to BCG to improve drug allocation by only administering BCG administration to those who are most likely to benefit from it. In addition, several ongoing trials are enrolling patients with BCG-naïve T1 HG NMIBC to receive checkpoint inhibitors (NCT04134000, NCT04165317) or intravesical immunotherapy or chemotherapy (NCT04386746) with the aim of providing a valid alternative to intravesical BCG, especially for patients at higher risk of progression despite adequate BCG therapy.

Tools currently available for prediction of outcomes in patients with T1 HG NMIBC are mainly based on standard clinicopathological features and suffer from limited predictive accuracy [2–4]. Several biomarkers have recently been investigated with the aim of improving the accuracy of existing tools, with mainly unsatisfactory results [5–8]. It has been shown that skeletal muscle loss (sarcopenia) can predict survival outcomes in several neoplasms, including genitourinary cancers [9–11]. However, almost all the studies assessing sarcopenia have been conducted in an advanced/metastatic disease setting, in which sarcopenia is probably reflective of a deterioration in patients' general clinical condition. In bladder cancer (BC), sarcopenia can predict long-term oncological outcomes in patients undergoing RC and those treated with platinum-based chemotherapy [10,12]. To date, however, the prognostic role of sarcopenia in NMIBC has not been investigated.

The aim of our study was to evaluate the ability of sarcopenia to predict recurrence-free survival (RFS) and progression-free survival (PFS) in a multicenter cohort of patients with T1 HG NMIBC treated with adjuvant BCG.

2. Patients and methods

This was an institutional review board–approved study, with all participating sites providing the necessary data-sharing agreements before initiation of the study. Records for patients with pathologically proven primary or recurrent completely resected T1 HG NMIBC treated with TURB and adjuvant intravesical immunotherapy with BCG between 2013 and 2017 at two tertiary referral centers were included in the study. For inclusion in the study, patients had to have a computed tomography (CT) scan performed within 2 mo from the surgery and complete data regarding follow-up.

None of the patients had upper tract urothelial carcinoma, prostatic stroma invasion, or metastatic BC at the time of surgery. After TURB, patients were treated according to international guidelines with adjuvant BCG immunotherapy (induction and maintenance). Usually, adjuvant treatment started after 7–21 d from TURB and was repeated once weekly for 6 wk. Repeat TURB (defined as a second-look resection performed within 2–6 wk after the first resection) was not routinely performed. Follow-up was performed according to international guidelines and usually consisted of urine cytology, ultrasound of the abdomen/pelvis, flexible cystourethroscopy, and cold biopsy/TURB of suspicious areas when appropriate. Imaging of the upper tract was usually carried out at diagnosis and yearly thereafter. If urine cytology was positive, mapping bladder biopsies, prostatic urethra resection, and upper urinary tract evaluation were performed.

Sarcopenia, identified from CT scans performed within 2 mo after surgery, was defined as a skeletal muscle index of <39 cm^2/m^2 for women and <55 cm^2/m^2 for men [13]. Axial CT images at the lumbar

vertebral level were used to measure skeletal muscle areas because the total lumbar-skeletal muscle cross-sectional area is linearly correlated to whole-body skeletal muscle mass [14]. The total skeletal muscle area at the third lumbar vertebra, including the psoas, paraspinal muscles (the erector spinae and quadratus lumborum), and abdominal wall muscles (transversus abdominus, external and internal obliques, and rectus abdominus), was measured using OsiriX imaging software (Pixmeo, Geneva, Switzerland). The Grow Region (2D/3D Segmentation) tool was used to automatically select all skeletal muscle mass in one transversal CT image. The cross-sectional area of skeletal muscle was identified using a Hounsfield unit threshold of −29 to +150. Manual adjustment for selected areas was performed if necessary.

2.1. Statistical analysis

Results are reported as the absolute number and percentage for categorical variables and as the median and interquartile range (IQR) for continuous variables. We performed χ^2 and Kruskal Wallis tests to compare categorical and continuous variables, respectively, between the groups. The main endpoint of the study was the association between sarcopenia and oncological outcomes such as RFS and PFS. Kaplan-Meier curves were built to evaluate differences in RFS, PFS, cancer-specific survival (CSS), and overall survival (OS) according to the presence of sarcopenia. RFS and PFS were defined as the time between T1 HG diagnosis and recurrence of NMIBC or progression to MIBC during follow-up, respectively. CSS and OS were defined as the time between T1 HG diagnosis and death from BC or other causes, respectively. The log-rank test was used to determine the significance of differences between groups. For RFS and PFS, patients were censored at the date of disease recurrence or progression or the last negative cystoscopy assessment. For CSS and OS, patients were censored at the date of death. Univariable and multivariable Cox models accounting for the effect of standard prognosticators were constructed to assess the association between sarcopenia and the outcomes. The multivariable model for PFS was restricted to four variables owing to the low number of events. Variables included in the multivariable model were chosen according to their known relation with the outcome of interest. Harrell's C index was calculated to evaluate the ability of sarcopenia to improve the discrimination of standard established models. The model was internally validated via bootstrapping (100 resamples). Finally, the clinical utility of the model was assessed using decision curve analysis (DCA) at 2 yr from diagnosis. The model with sarcopenia was compared to the strategies of treating none and treating all patients with early RC, and to a standard model based on established clinicopathological features. The clinical net benefit was calculated for each probability threshold. Statistical analyses were performed using Stata v16 (Stata Corp., College Station, TX, USA). All tests were two-sided and $p < 0.05$ was considered statistically significant.

3. Results

The patient characteristics at baseline are listed in Table 1. Overall, 185 patients with T1 HG NMIBC treated with BCG were included in the study. Of these, 155 (84%) were male and 30 (16%) were female. The median age at the time of enrollment was 71 yr (IQR 64–78). The majority of patients (83%) presented with primary T1 HG NMIBC; the median number of recurrences among recurrent cases was 1 (IQR 0–1). Sixty-nine patients (39%) harbored multifocal tumors, and 57 (35%) presented with a tumor of ≥3 cm in size. Concomitant carcinoma in situ (CIS) was found in 57 patients (32%). Sarcopenia was identified in 130 patients (70%; Fig. 1).

Table 1 – Descriptive characteristics of the cohort of 185 patients with T1 high-grade non–muscle-invasive bladder cancer treated with transurethral resection of the bladder and adjuvant intravesical bacillus Calmette-Guérin

Parameter	Preoperative sarcopenia		*p* value
	No	Yes	
Patients, *n* (%)	55 (30)	130 (70)	
Median age, yr (interquartile range)	66 (57–73)	74 (66–79)	<0.001
Sex, *n* (%)			<0.001
Female	21 (38)	9 (7)	
Male	34 (62)	121 (93)	
Median body mass index, kg/m^2 (interquartile range)	28 (26–31)	26 (24–28)	<0.001
Smoking habit, *n* (%)			0.3
Never smoker	11 (23)	25 (25)	
Former smoker	17 (35)	46 (46)	
Current smoker	20 (42)	28 (28)	
Recurrent tumor, *n* (%)	9 (16)	22 (17)	0.9
Median number of recurrences, *n* (interquartile range)	0.5 (0–1)	1 (1–1)	0.07
Concomitant carcinoma in situ, *n* (%)	17 (32)	40 (33)	0.9
Tumor size, *n* (%)			0.5
<3 cm	34 (69)	74 (64)	
≥3 cm	15 (31)	42 (36)	
Multifocal tumor, *n* (%)	21 (40)	48 (39)	0.8
Macroscopic appearance, *n* (%)			0.9
Papillary	32 (63)	65 (55)	
Solid	19 (37)	53 (45)	
Second-look resection, *n* (%)	23 (42)	60 (46)	0.6
Median skeletal muscle index, cm^2/m^2 (interquartile range)	57 (46–60)	46 (40–51)	<0.001
Females	44 (40–50)	32 (29–34)	
Males	59 (56–64)	46 (41–51)	

3.1. Oncological outcomes

Median follow-up for patients alive at last follow-up was 31 mo (IQR 21–43). During this time, 84 patients experienced disease recurrence and 34 developed disease progression. Overall, there were 41 deaths, of which 15 were related to BC. The 1-yr and 3-yr RFS rates were 60% and 51% for patients with sarcopenia, and 68% and 54% for those without sarcopenia, respectively ($p = 0.5$). Median RFS was 13 mo (IQR 5–31). The 1-yr and 3-yr PFS rates were 80% and 75% for patients with sarcopenia, and 96% and 91% for those without sarcopenia, respectively ($p = 0.03$). Median PFS was 26 mo (IQR 9–40). The 1-yr and 3-yr CSS rates were 97% and 88% for patients with sarcopenia, and 100% and 100% for patients without sarcopenia, respectively ($p = 0.06$). The 1-yr and 3-yr OS rates were 94% and 81% for patients with sarcopenia, and 100% and 86% in patients without sarcopenia, respectively ($p = 0.09$; Fig. 2).

3.2. Prediction of oncological outcomes

On univariable Cox-regression analyses, smoking habit, recurrent tumor, and concomitant CIS were significant predictors of RFS. Sarcopenia was not associated with disease recurrence (hazard ratio [HR] 1.17, 95% confidence interval [CI] 0.73–1.89; $p = 0.59$). Evaluation of PFS revealed that body mass index and sarcopenia were significantly associated with disease progression (HR 2.72, 95% CI 1.05–7.02; $p = 0.04$). On multivariable analyses adjusted for the effect of standard prognosticators, gender, smoking habit, and recurrent tumor were significantly associated with RFS, while concomitant CIS and sarcopenia (HR 3.41, 95% CI 1.17–9.93; $p = 0.02$)

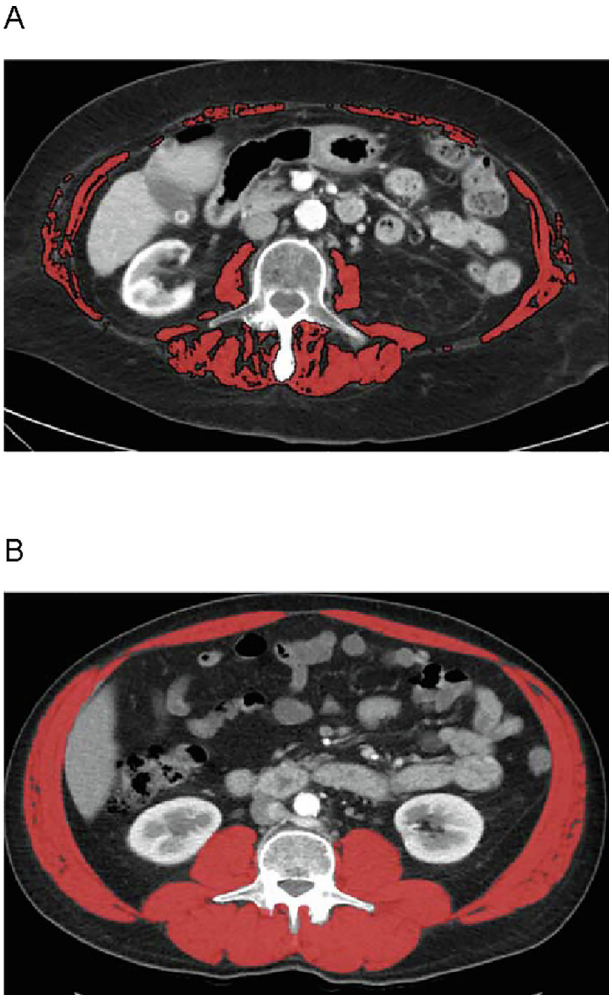

Fig. 1 – Computed tomography images at the level of the third lumbar vertebra highlighting (in red) the total skeletal muscle area (including the psoas, paraspinal muscles and abdominal wall muscles) in (A) a patient with sarcopenia and (B) a patient without sarcopenia.

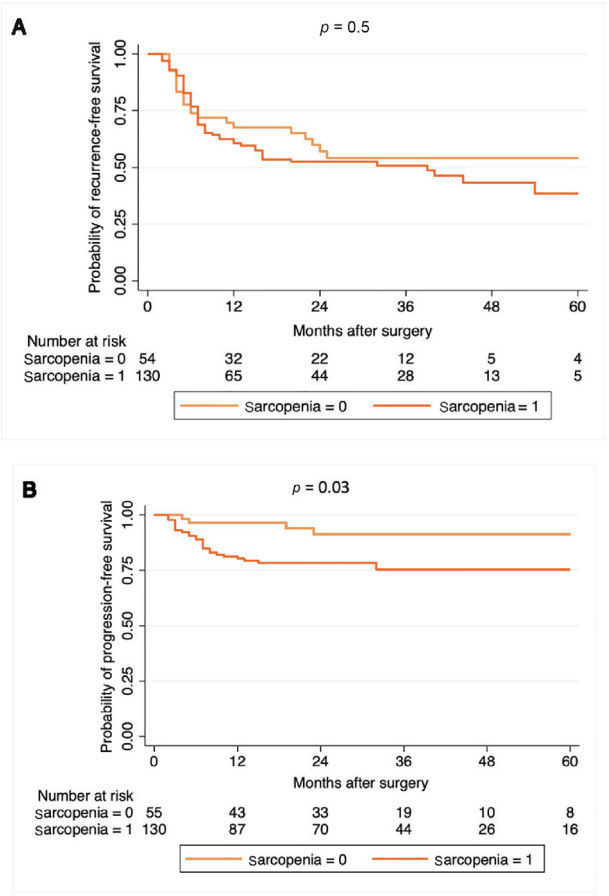

Fig. 2 – Kaplan-Meier estimates for (A) recurrence-free survival, (B) progression-free survival, (C) cancer-specific survival, and (D) overall survival according to sarcopenia status among 185 patients with T1 high-grade non–muscle-invasive bladder cancer treated with transurethral resection of the bladder and adjuvant bacillus Calmette-Guérin.

significantly predicted disease progression (Table 2). Harrell's C index for prediction of disease progression was 0.62 for a model based on standard clinicopathological variables [3]. Addiction of sarcopenia to this model improved Harrell's C to 0.70. Bootstrap-corrected discrimination of the prognostic model did not differ from the original one.

In the DCA for disease progression at 2 yr, our sarcopenia-based model provided a net benefit across a large group of threshold probabilities (from 0% to 20%) in comparison to a model based on the variables included in the European Organisation for Treatment and Research of Cancer (EORTC) risk tables (age, tumor status, focality, size, concomitant CIS). Moreover, our model was able to improve decision-making in comparison to the strategies of treating all or no patients with early RC (Fig. 3). The net reduction in interventions as a function of the threshold probability is depicted in Figure 4.

4. Discussion

In our multicenter retrospective study, more than two-thirds of patients with T1 HG NMIBC treated with adjuvant BCG had sarcopenia. The term *sarcopenia* was first coined by Irwin Rosenberg in 1989, derived from the terms *sarx* and *penia* (flesh and loss in Greek), to describe the age-related decrease in muscle mass [15]. Sarcopenia, representing degenerative and systemic loss of skeletal muscle mass, is a multifactorial syndrome caused by a mix of several different conditions that include aging, physical inactivity, malnutrition, neuromuscular disorders, inflammatory or endocrine diseases, and malignancies [16]. In cancer, skeletal muscle depletion and weight loss are hallmarks of cachexia and are usually associated with poor prognosis. This could be the result of both tumor and host factors. On one hand, the shift towards a catabolic state because of anorexia, poor nutrition, and systemic inflammation may be directly related to cancer aggressiveness, while on the other hand, patients with sarcopenia carry a higher risk of falls and fractures, have higher rates of cardiovascular comorbidities, and are more susceptible to suffering from infectious diseases, metabolic syndrome, and insulin resistance, and are therefore at higher risk of succumbing to their cancer [17].

A growing body of evidence has shown the prognostic role of sarcopenia in various malignancies, including urological tumors [9,11,18–21]. In urothelial cancer, sarcopenia

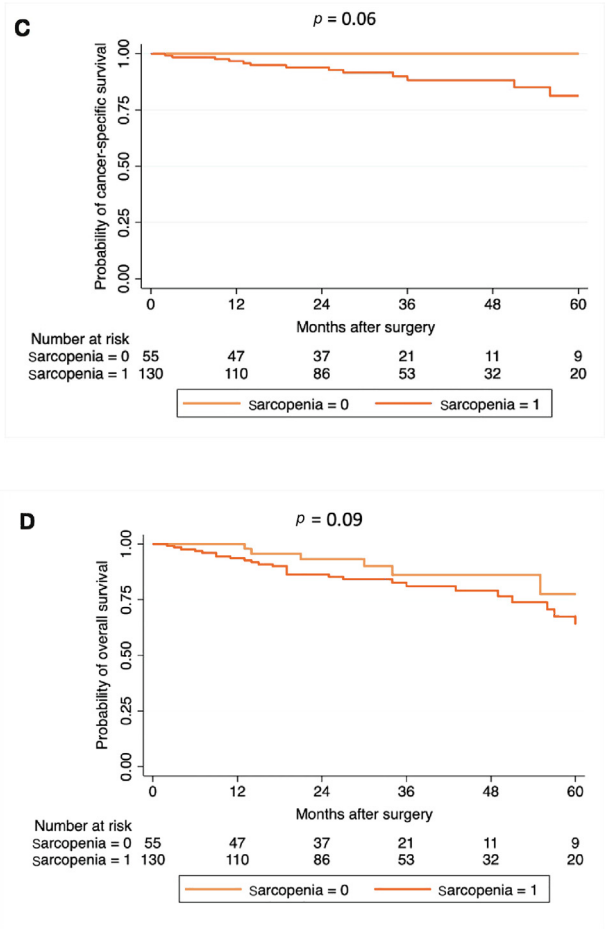

Fig. 2 (*continued*)

has been associated with perioperative mortality and complications, as well as with CSS and OS, among patients undergoing RC for BC [22,23]. However, to the best of our knowledge, no studies have investigated the role of sarcopenia in NMIBC so far.

We found that the presence of sarcopenia independently predicted progression to muscle-invasive disease in patients with T1 HG NMIBC treated with adjuvant BCG. Moreover, we showed that addition of sarcopenia to a standard model for prediction of disease progression based on the EORTC risk tables increased the accuracy of the model from 66% to 72%, with several practical implications. Predicting disease progression in patients with T1 HG NMIBC is of fundamental importance for decision-making regarding early RC and BGC allocation, especially in times of BCG shortage. To date, several biomarkers have been investigated as predictors of response to BCG in this population, with mainly unsatisfactory results because of insufficient inaccuracy, lack of external validation and reproducibility, and high costs. Conversely, sarcopenia is a readily available and cost-free biomarker as it can be easily and rapidly measured via a CT scan of the abdomen performed in the perioperative setting, as recommended by international guidelines for HG NMIBC cases [24].

Several limitations should be considered. We acknowledge the presence of selection biases inherent to the retrospective design of the study. We could not account for performance status, patient comorbidities, surgeon experience, or other unmeasurable confounders. We were not able to assess the role of subsequent therapies after BCG that may have contributed to the impact on long-term oncological outcomes such as CSS and OS. There was no central pathology review of the specimens. Almost half of the patients did not undergo second-look resection, which is recommended by international guidelines, with a possible impact on disease persistence and upstaging. However, we tried to mitigate this effect by including the lack of second-look resection in our multivariable models. The relatively short follow-up might have prevented detection of a significant association between sarcopenia and survival. Finally, the biological association of sarcopenia with adverse outcomes in NMIBC is not completely explainable, and our study is the first report describing such an association for sarcopenia in a "nonadvanced" disease setting. We hypothesize that this association might be explained by the intrinsic aggressiveness of the disease or by the presence of micrometastatic dissemination (not as uncommon in T1 HG disease).

Despite all these limitations and pending external validation, sarcopenia could be integrated into current models

Table 2 – Multivariable Cox proportional-hazard regression analyses for the prediction of recurrence-free and progression-free survival among 185 patients with T1 high-grade non–muscle-invasive bladder cancer treated with transurethral resection of the bladder and adjuvant intravesical bacillus Calmette-Guérin

Parameter	Recurrence-free survival		Progression-free survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (continuous)	1.00 (0.97–1.03)	0.9		
Female (vs male)	2.76 (1.15–6.60)	0.02		
Body mass index (continuous)	0.95 (0.88–1.03)	0.2		
Smoking habit (vs never smoker)				
Former smoker	2.42 (0.98–5.97)	0.06		
Current smoker	2.46 (1.00–6.03)	0.05		
Recurrent tumor (vs primary tumor)	2.31 (1.10–4.87)	0.03		
Concomitant carcinoma in situ	1.61 (0.86–3.04)	0.1	2.82 (1.33–5.99)	0.007
Tumor size ≥3cm (vs <3cm)	1.27 (0.64–2.55)	0.5	0.58 (0.26–1.28)	0.2
Multifocal tumor (vs single tumor)	1.78 (0.91–3.49)	0.09	0.65 (0.30–1.39)	0.3
Macroscopic solid appearance (vs papillary)	0.72 (0.58–2.07)	0.8		
Second-look resection (vs none)	1.09 (0.58–2.07)	0.8		
Sarcopenia	1.59 (0.78–3.25)	0.2	3.41 (1.17–9.93)	0.02

CI = confidence interval; HR = hazard ratio.

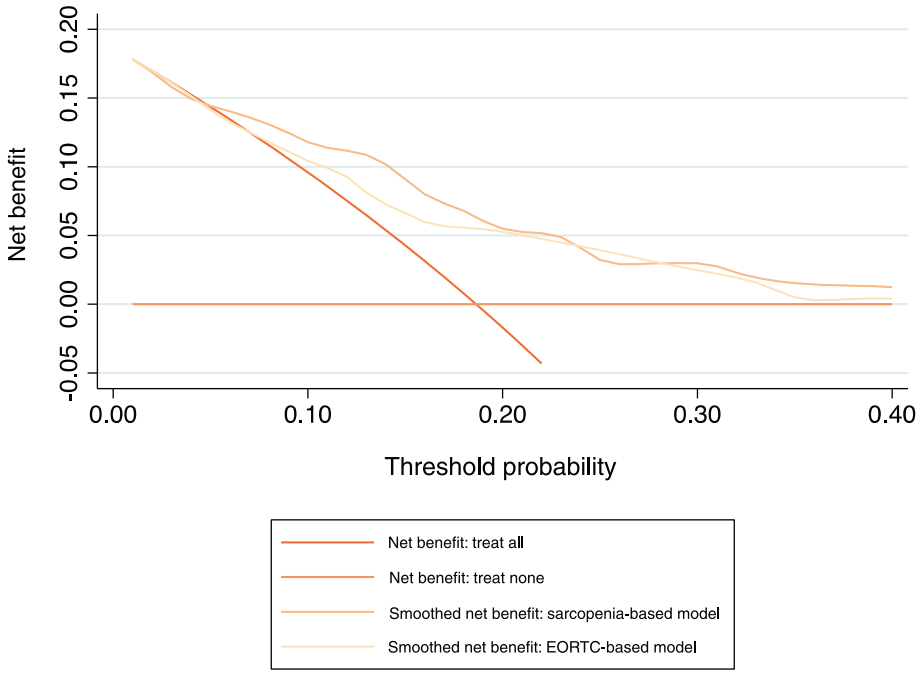

Fig. 3 – Decision curve analysis of the clinical impact of the new sarcopenia-based model over the existing EORTC-based model for estimating the probability of disease progression in the cohort of 185 patients with T1 high-grade non–muscle-invasive bladder cancer treated with transurethral resection and adjuvant bacillus Calmette-Guérin. The sarcopenia-based model is compared to the EORTC-based model and to strategies of treating none or treating all patients with early radical cystectomy. EORTC = European Organisation for Treatment and Research of Cancer.

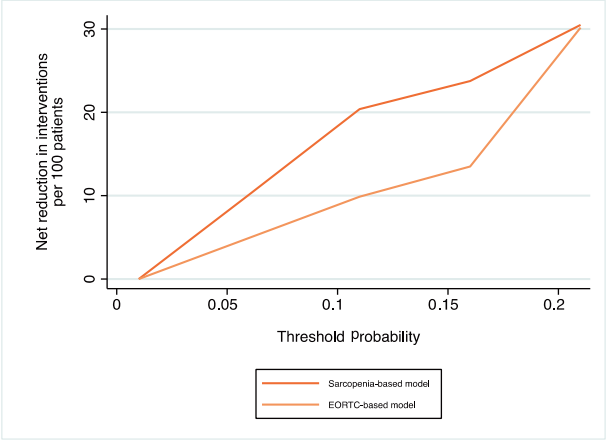

Fig. 4 – Net reduction in interventions per 100 patients and related threshold probabilities according to the decision curve analysis. EORTC = European Organisation for Treatment and Research of Cancer.

to improve outcome predictions and could serve as a rationale in patient counseling and for decision-making regarding treatment.

5. Conclusions

Sarcopenia was identified in two-thirds of patients with T1 HG NMIBC treated with BCG and was an independent predictor of progression to muscle-invasive disease. Its addition to an existing model based on established clinicopathological variables improved the accuracy of the model in predicting disease progression. Pending external validation, sarcopenia could be added to current prognosticators for decision-making for patients with T1 HG NMIBC.

Author contributions: Francesco Soria had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Soria, D'Andrea.
Acquisition of data: Barale, Gust, Pisano, Mazzoli, De Bellis, Rosazza, Livoti, Dutto, Lillaz, Tamandl.
Analysis and interpretation of data: Soria.
Drafting of the manuscript: Soria, Barale.
Critical revision of the manuscript for important intellectual content: Moschini, Pradere, Shariat, Gontero.
Statistical analysis: Soria.
Obtaining funding: None.
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Supervision: Shariat, Gontero.
Other: None.

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