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## INVITED REVIEW

Prostate Cancer

# Radical prostatectomy in patients aged 75 years or older: review of the literature

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Given the demographic trends toward a considerably longer life expectancy, the percentage of elderly patients with prostate cancer will increase further in the upcoming decades. Therefore, the question arises, should patients  $\geq 75$  years old be offered radical prostatectomy and under which circumstances? For treatment decision-making, life expectancy is more important than biological age. As a result, a patient's health and mental status has to be determined and radical treatment should only be offered to those who are fit. As perioperative morbidity and mortality in these patients is increased relative to younger patients, patient selection according to comorbidities is a key issue that needs to be addressed. It is known from the literature that elderly men show notably worse tumor characteristics, leading to worse oncologic outcomes after treatment. Moreover, elderly patients also demonstrate worse postoperative recovery of continence and erectile function. As the absolute rates of both oncological and functional outcomes are still very reasonable in patients  $\geq 75$  years, a radical prostatectomy can be offered to highly selected and healthy elderly patients. Nevertheless, patients clearly need to be informed about the worse outcomes and higher perioperative risks compared to younger patients.

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**Keywords:** age; functional outcome; oncological outcome; prostate cancer; radical prostatectomy

## INTRODUCTION

Prostate cancer (PCa) is the most frequent cancer among males in developed countries and a leading cause of cancer deaths.<sup>1,2</sup> Due to the increasing life expectancy of men worldwide, the percentage of elderly patients who are more likely to develop PCa will increase further within the next few decades. This will lead to an intensified discussion about age limits for radical treatment in patients with PCa.<sup>3,4</sup> The recently updated International Society of Geriatric Oncology (SIOG) guidelines on PCa in men aged  $>70$  years advise a mandatory health screening using the G-8 tool and mini-COG<sup>TM,5,6</sup> and to offer fit elderly men (e.g., with a G-8 of  $>14$  points) the same treatment options as younger men, as patients should not be treated according to their biologic age but according to their individual health status.<sup>7</sup> When considering elderly patients for radical prostatectomy (RP), life expectancy (LE), and perioperative morbidity and mortality, oncologic and functional outcomes are important factors to consider. Despite current studies reporting reasonable oncologic and functional outcomes, patients 75 years or older with PCa are still subject to undertreatment.<sup>8–10</sup> The aim of this review is to summarize the literature on RP in men older than 75 years and to give an overview of the risks, benefits, and proper selection in this special cohort of patients.

A literature review was performed using PubMed and Medline databases. Electronic articles published ahead of print were also included. The search focused on articles in English and was completed

using the following keywords: radical prostatectomy, elderly patients, outcomes, age, prostate cancer, and  $\geq 75$  years.

## IMPORTANT SELECTION CRITERIA FOR RP IN THE ELDERLY PATIENTS

### *LE and the risk of dying from noncuratively treated PCa*

Present guidelines for the treatment of PCa request a suitable remaining LE for patients undergoing RP, but do not have a certain age limit (European Association of Urology [EAU] guideline: LE  $>10$  years; National Comprehensive Cancer Network [NCCN] guideline: LE 10–20 years depending on risk group; American Urological Association [AUA] guideline: a “reasonable” LE).<sup>11–13</sup> Men aged 75 years in developed countries have an additional LE of 10 years,<sup>14–16</sup> which increases to 15 years when looking at the top 25<sup>th</sup> percentile of the healthiest men.<sup>17</sup> As a result, more elderly men are suitable for RP according to current guidelines. Thereby, a health screening in all patients  $>70$  years old using the G-8 tool<sup>5</sup> and mini-COG<sup>TM6</sup> has been suggested.<sup>7</sup> RP should only be offered to fit elderly men (e.g., with a G-8 score of  $>14$  points). Screening with G-8 can also help to decide whether further Comprehensive Geriatric Assessment (CGA) is indicated to identify potentially reversible conditions. Moreover, it is known that for poorly differentiated PCa, potentially curative therapy can lead to an increase not only in LE but also quality-adjusted LE in patients up to the age of 80 years.<sup>18</sup> Rider *et al.*<sup>19</sup> showed 10-year cancer-specific mortality (CSM) rates among men older than 75 years with intermediate- or high-risk PCa treated with noncurative intent to

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be 14.9% and 29.4%, respectively, while 10-year other cause mortality rates (OCM) constantly decreased to approximately 50% with lower Charlson Comorbidity Index (CCI). Populations undergoing RP and noncurative treatment should still only be compared with great caution since patients above 75 years of age undergoing RP are a highly selected population.

For patients with age  $\geq 75$  years with locally advanced tumors, cancer-specific mortality without curative treatment is even higher (up to 40% after 8 years).<sup>20</sup> Nevertheless, some authors report that only 10% of men with high-risk PCa between 75 and 80 years of age and a CCI of 0 receive radical treatment despite a 52% probability of a 10-year LE.<sup>21</sup> This undertreatment of elderly patients might be due in part to the fact that physicians frequently underestimate 10-year LE.<sup>22–26</sup> Moreover, some urologists still avoid definitive treatment for localized PCa in elderly patients because of age alone.<sup>27,28</sup> In an analysis of a large cohort of patients undergoing RP, after age, CCI was the factor with the strongest influence on OCM in elderly patients.<sup>29</sup> Nevertheless, age alone should not be a contraindication for RP in patients 75 years or older, especially in men with high-risk disease and no other relevant comorbidities, as both LE and risk of death due to a noncuratively treated PCa are high in these patients. Therefore, an evaluation of LE by analyzing comorbidities (e.g., using CCI) should be mandatory when selecting elderly patients for surgery to identify particularly healthy individuals for RP.<sup>30–32</sup>

#### Tumor characteristics

It is known that elderly patients diagnosed with PCa show more aggressive and locally advanced tumors.<sup>27,28,33–37</sup> Patients 75 years or older undergoing RP have high-risk disease in 25% of cases and nonorgan-confined tumor in up to 50% of cases in the final pathology.<sup>36</sup> It is questionable if these advanced tumor characteristics in elderly patients are solely attributable to the natural history of PCa rather than to patient selection. Certainly, patients older than 75 years are less likely to undergo PSA testing and biopsy and will, also due to a higher risk of perioperative mortality and morbidity (see below), not routinely undergo RP in cases with a very low risk of disease progression. Radical treatment is often avoided in patients above the age of 75 years despite harboring high-risk disease.<sup>21</sup>

#### Perioperative morbidity and mortality

Perioperative morbidity and mortality was often identified as a potential reason against performing RP in elderly patients in the past.<sup>38</sup> Alibhai *et al.*<sup>39</sup> analyzed data from 11 010 men who underwent surgery in Ontario, Canada, between 1990 and 1999. Overall, the risk of death was 0.48% and the risk of complications within 30 days of RP was 20.4%. Nevertheless, although age was still associated with an increased risk of 30-day mortality and medical complications after controlling for comorbidities, the absolute numbers were still favorable in elderly patients (0.66% risk of death, 26.9% risk of complications for men aged 70–79 years). A similar study by Begg *et al.*<sup>40</sup> assessing

the perioperative morbidity and mortality rates among 11 522 men undergoing RP in the United States between 1992 and 1996 showed the risk of at least one postoperative complication to be 28%, 31%, and 35% and the risk of 30-day mortality to be 0.4%, 0.5%, and 0.9% for men aged 65–69 years, 70–74 years, and 75 years and older, respectively. An increase in 30-day mortality with increasing CCI was also seen (0.3%, 0.8% and 1.6% for CCI of 0, 1 and 2 or above, respectively). When comparing RP with external beam radiation therapy (EBRT), differences in perioperative mortality favoring EBRT increased with higher age and CCI. For example, in patients above 75 years, differences in 30-day (90-day) mortality between RP and EBRT ranged from 0.4% to 1.1% (2.1%–3.2%), depending on their CCI.<sup>41</sup> However, both radiotherapy and androgen deprivation therapy have significant side effects, particularly in older men (gastrointestinal and genitourinary for radiation therapy, cardiovascular events for androgen deprivation therapy), which should not be underestimated in treatment decision making.<sup>42,43</sup>

Patients 75 years or older with higher CCI do have an increased risk of perioperative morbidity and mortality as compared to younger and healthier men and should be counselled about this fact prior to RP.

#### Oncologic outcomes

While the body of literature analyzing oncologic outcomes after RP in patients above the age of 65 and 70 years is large,<sup>34,44–49</sup> only a few studies specifically focus on patients  $\geq 75$  years (Table 1).<sup>27,36,50,51</sup> Due to small sample sizes and short follow-up in some studies, oncologic results (biochemical recurrence [BCR], metastasis-free and cancer-specific survival [CSS]) are incompletely reported with only limited comparability.

Labanaris *et al.*<sup>27</sup> published results of 45 patients  $\geq 75$  years undergoing robotic-assisted laparoscopic RP. After a median follow-up of 17.2 months, no disease-specific deaths were recorded and 95.5% were free of biochemical progression. The reported oncological outcomes were limited by short median follow-up and small sample size. Another study by Xylinas *et al.*<sup>50</sup> analyzed 22 patients who underwent laparoscopic RP with a median follow-up of 45.0 months. No patient died within the follow-up and 5-year BCR-free survival was around 70%. Ryu *et al.*<sup>51</sup> published their results comparing 89 patients  $\geq 75$  years to 168 younger patients between 65 and 69 years with a median follow-up of 40.0 months. After 5 years, BCR-free survival in the group of elderly patients was approximately 86% and not statistically different to younger patients (approximately 87.5%). No information on metastasis-free survival and CSS was provided. The largest study to date analyzing the oncologic outcome of patients  $\geq 75$  years was published by our group. We compared 265 patients  $\geq 75$  years to 13 732 patients  $< 75$  years of age with a median follow-up of 47.3 months.<sup>36</sup> Five-year BCR-free, metastasis-free survival, CSS, and overall survival (OS) rates were 64.2%, 84.7%, 98.4%, and 91.3% for the older group and 76.9%, 96.2%, 99.0%, and 96.2% for the younger patients, respectively. The lower 5-year BCR-free

**Table 1: Oncologic outcome in patients  $\geq 75$  years undergoing radical prostatectomy**

Study	Year	Comparison group	Number of patients $\geq 75$ years included/number of comparison group (n/n)	Median FU (months)	BCR-free survival	Metastasis-free survival	Cancer-specific survival
Xylinas <i>et al.</i> <sup>50</sup>	2010	–	22/–	45.0	70% (5 years)	–	100%
Labanaris <i>et al.</i> <sup>27</sup>	2012	All patients undergoing RP irrespective of age	45/2000	17.2	95.5% at median FU	–	100%
Ryu <i>et al.</i> <sup>51</sup>	2016	Patients 65–69 years	89/168	40.0	86% (5 years)	–	–
Mandel <i>et al.</i> <sup>36</sup>	2016	Patients $< 75$ years	265/13 732	47.3	64.2% (5 years)	84.7% (5 years)	98.4% (5 years)

BCR: biochemical recurrence; FU: follow-up; RP: radical prostatectomy



survival rates, especially compared to the data from Ryu *et al.*,<sup>51</sup> can be attributed to the lower rate of organ-confined tumors in the cohort of patients  $\geq 75$  years of age in our study (54.2% vs 64.0%). In univariable analysis, older patients were more likely to develop BCR (HR: 1.74,  $P = 0.001$ ) and metastases (HR: 3.14,  $P = 0.002$ ).<sup>36</sup> After adjusting for adverse tumor characteristics of older patients in multivariable analysis, the effect of age remained significant for both BCR (HR: 2.13, 95% CI: 1.53–2.95,  $P < 0.001$ ) and metastases (HR: 1.91, 95% CI: 1.03–3.53,  $P = 0.040$ ). Age at the time of RP did not influence CSS in univariable or multivariable regression (both  $P > 0.05$ ).

Recently published data for men  $\geq 75$  years with initial conservative treatment for newly diagnosed localized PCa reported CSM rates after 15-year of 10%–27%, depending on Gleason score.<sup>52</sup> Comparing these survival rates with the ones after RP, elderly patients might benefit from RP compared to conservative treatment, especially when harboring high-risk PCa despite their worse results after RP compared to younger patients.<sup>53</sup> Therefore, from an oncologic standpoint, age alone should not be a contraindication for RP in carefully selected men  $\geq 75$  years. Good patient selection

in elderly patients is currently already reflected by low other cause mortality in these patients in large RP series.<sup>29</sup>

### Functional outcomes

There is evidence in literature that increasing age is a risk factor for worse functional outcome after RP.<sup>17,27,33,34,50,51,54–57</sup> An overview of studies reporting functional outcomes after RP in patients  $\geq 75$  years is depicted in **Table 2**. Most current studies defined continence as the use of no pads and an erection sufficient for intercourse as potent. Labanaris *et al.*<sup>27</sup> reviewed the records of 2000 patients who underwent RP, in whom 45 patients were 75 years or older. While the authors showed no significant difference in achieving continence after 12 months (92.8% younger patients vs 86.9% elderly patients,  $P > 0.05$ ), the difference between age groups in postoperative potency in men with bilateral nerve sparing (66.2% vs 39.6%,  $P < 0.001$ ) was statistically significant. No multivariable analyses were performed. Xylinas *et al.*<sup>50</sup> analyzed the functional outcomes of 22 men  $\geq 75$  years after RP and reported very similar rates (12-month continence rate of 82% and 12-month potency rate of 36% with or without the use

**Table 2: Functional outcome in patients  $\geq 75$  years undergoing radical prostatectomy**

Study	Year	Comparison group	Number of patients $\geq 75$ years included/number of comparison group (n/n)	Definition of continence	Definition of potency	Continence	Potency
Xylinas <i>et al.</i> <sup>50</sup>	2010	–	22/–	Pad-free	Erection sufficient for intercourse	12-month continence rate of 82%	12-month potency rate of 36% with or without the use of phosphodiesterase-5 inhibitors
Shikanov <i>et al.</i> <sup>56</sup>	2010	Age as continuous variable, point estimates at 65, 70 and 75 years	Overall 1436	Pad-free	Erection sufficient for intercourse	Significant influence of age (as continuous variable) on 12-month continence (OR: 0.97, $P=0.002$ ) with point estimates of continence at 65, 70, and 75 years being 0.66, 0.63, and 0.59, respectively	Significant influence of age (as continuous variable) on 12-month potency (OR: 0.92, $P<0.0001$ ) with point estimates of potency at 65, 70, and 75 years after bilateral nerve sparing being 0.66, 0.56, and 0.46, respectively
Labanaris <i>et al.</i> <sup>27</sup>	2012	All patients undergoing RP irrespective of age	45/2000	Pad-free	Erection sufficient for intercourse	Insignificant difference in 12-month continence between age groups (92.8% vs 86.9%, $P>0.05$ )	Significant difference in postoperative potency between age groups (66.2% vs 39.6%, $P<0.001$ [only patients with bilateral nerve sparing were included for potency analysis])
Mandel <i>et al.</i> <sup>17</sup>	2015	$\geq 70$ and $< 75$ , $\geq 65$ and $< 70$ , $< 65$ years	166/1597/2344/4188	0 or 1 safety pad per day	IIEF-5 score $\geq 18$ or erection sufficient for intercourse	3-month continence was 66.1%, 70.3%, 74.0%, 80.3%, respectively ( $P<0.001$ ); 12 months: 86.5%, 86.0%, 90.8%, 93.3%, respectively ( $P<0.001$ ). Age was a significant factor influencing continence after 3 and 12 months in multivariable analysis	Potency rates (bilateral nerve-sparing) at 12 months were 33.3%, 50.6%, 49.5%, 61.6% ( $P<0.001$ , IIEF-5) and 37.5%, 49.0%, 54.0%, 70.3% ( $P<0.001$ , erection sufficient for intercourse). Age was a significant factor influencing potency after 3 and 12 months in multivariable analysis
Ryu <i>et al.</i> <sup>51</sup>	2016	Patients 65–69 years	89/168	0 or 1 safety pad per day	Erection sufficient for intercourse	At 3 months after RP, 37.5% in the younger group and 18.0% in the older group were continent ( $P<0.001$ ); by 12 months, these rates increased to 85.7% and 76.4%, respectively ( $P=0.084$ ). Elderly patients had a significantly longer time to achieve continence	Rate of postoperative erectile dysfunction was not significantly different within groups (52.4% vs 44.9%, $P=0.295$ )

IIEF: International Index of Erectile Function; OR: odds ratio; RP: radical prostatectomy

of phosphodiesterase-5 inhibitors). A comparison to functional outcomes of younger patients was not provided by the authors. Ryu *et al.*<sup>51</sup> compared their results of 89 patients  $\geq 75$  years to 168 younger patients between 65 and 69 years. Continence was defined as the use of  $\leq 1$  safety pad per 24 h. At 3 months after RP, 37.5% of younger vs 18.0% of elderly patients were continent. After 12 months, the continence rates increased and were not significantly different between younger and older patients (85.7% vs 76.4%,  $P = 0.084$ ). However, in multivariable analyses, older patients needed longer time to achieve continence after RP ( $P = 0.016$ ). Concerning potency, the authors reported no significant difference in the rate of postoperative erectile dysfunction (ED) between the two groups (52.4% vs 44.9%,  $P = 0.295$ ). In the largest cohort of patients  $\geq 75$  years so far, we analyzed the functional outcome of 166 patients  $\geq 75$  years and compared them to patients  $\geq 70$  and  $< 75$  years ( $n = 1597$ ),  $\geq 65$  and  $< 70$  years ( $n = 2344$ ), and  $< 65$  years ( $n = 4188$ ).<sup>17</sup> Similar to Ryu *et al.*,<sup>51</sup> patients were considered continent if  $\leq 1$  safety pad per 24 h was used. After 3 and 12 months, elderly patients showed reasonable continence rates; nevertheless, these rates were lower compared to younger patients (3-month continence: 66.1%, 70.3%, 74.0%, and 80.3%,  $P < 0.001$ ; 12-month continence: 86.5%, 86.0%, 90.8%, and 93.3%,  $P < 0.001$ ; for patients  $\geq 75$ ,  $\geq 70$  and  $< 75$ ,  $\geq 65$  and  $< 70$ ,  $< 65$  years, respectively). The respective potency rates after 12 months in patients with bilateral nerve sparing procedure were 37.5%, 49.0%, 54.0%, and 70.3% ( $P < 0.001$ ) if erection sufficient for intercourse was used as a definition for potency. If an international index of erectile function (IIEF-5) score  $\geq 18$  was used as the definition, 33.3%, 50.6%, 49.5%, and 61.6% ( $P < 0.001$ ) achieved potency, respectively. Age was a significant factor influencing recovery of continence and potency after 3 and 12 months in multivariable analysis. Both continence and potency can further improve after the threshold of 12 months (up to 50% of patients who suffer from incontinence and 36% of patients with ED after 12 months recover within the next 24 months). Age remains a significant factor influencing late recovery of functional outcome.<sup>58</sup>

Although absolute chances for recovery of continence and potency in patients  $\geq 75$  years at RP are reasonable, older age has a significant adverse effect. As ED becomes less important to patients with increasing age, and baseline ED is very common in patients  $\geq 75$  years without RP (up to 77%), the comparably low rates of potency after RP in patients  $\geq 75$  years may not be seen as a too strong argument against surgery.<sup>59,60</sup> Nevertheless, elderly patients clearly need to be informed about the increased risk of incontinence and ED after RP.

## CONCLUSIONS

Biological age  $\geq 75$  years alone should not be a strict contraindication for RP, as patients currently aged 75 years have an LE of  $> 10$  years and show reasonable functional and oncologic outcomes. However, a health screening in all elderly patients before RP is mandatory. Elderly patients with PCa harbor notably worse tumor characteristics. Older patients, particularly those with high-risk PCa, still benefit from radical treatment. Importantly, these patients need to be informed about the worse functional outcomes compared to younger patients. Moreover, perioperative morbidity and mortality is increased in elderly patients, so patient selection according to comorbidities is an important issue that needs to be addressed. Under these circumstances, RP in well-selected patients  $\geq 75$  years remains a feasible management option.

## AUTHOR CONTRIBUTIONS

PM drafted the manuscript and reviewed literature. TC, FKC, and HH edited the manuscript. DT drafted the manuscript, edited the

manuscript, and supervised the whole work. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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