SCANDINAVIAN JOURNAL OF UROLOGY
2022, VOL. 56, NO. 4, 334–335
https://doi.org/10.1080/21681805.2022.2107068

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LETTER TO THE EDITOR

Bladder cancer with secondary muscle invasion – a prognostic dilemma

Dear Editor,

With great interest we have read the excellent manuscript by Møller et al. in which survival rates of patients with bladder cancer (UCB) and primary muscle invasion (primMI) were compared to those of patients with secondary muscle invasion (secMI) [1]. For this purpose, the authors analyzed 650 patients within the Cancer Registry of Norway treated with curative intent from 2008 to 2012. The vast majority underwent radical cystectomy (RC; $n = 556$, 86%). In the RC group, 506 patients (91%) had primMI. This relatively high percentage (compared to international literature) was partly explained by the assignment of patients primarily diagnosed with non-muscle-invasive UCB to the primMI group if they progressed to muscle-invasive stage within $\leq$4 months after initial diagnosis. Within the RC group, cancer-specific mortality (CSM) at 5 years was 42% and 41% for patients with primMI and secMI, respectively, with no significant difference (HR: 0.93, $p = .78$).

Available data comparing prognosis of patients with primMI vs. secMI following RC was concisely discussed by Møller et al. and is summarized here again (Table 1) [2–13]. The majority of these studies confirm these findings from Norway showing no differences in survival rates. However, a recent multicentre study of 572 patients undergoing RC without neoadjuvant chemotherapy demonstrated higher 5-year-CSM rates for secMI compared to primMI (53.5 vs. 35.5%, $p < .001$) [12]. In a paper published more than 10 years ago in the *Scandinavian Journal of Urology* including 607 patients treated with RC for cT1 UCB, we demonstrated a 5-year-CSM of 24% for this group, although slightly more than one third of these patients showed an upstaging in the RC specimen ($\geq$pT2,pN0 or pTany,pN+) [14]. However, it is also undoubted that a general indication for early RC in all patients with high-risk nmiUCB represents an overtreatment in about two-thirds of patients, who persistently survive without tumor progression under conservative therapy [15,16].

Thus, two therapeutic avenues remain to overcome this dilemma. Firstly, more effective conservative therapies for patients with high-risk nmiUCB could result in fewer patients progressing to muscle invasion. Secondly, valid parameters predicting later progression to muscle invasion under conservative therapy for high-risk nmiUCB would allow these patients to be referred to curatively intended therapy (RC or radiochemotherapy) already before secMI becomes evident. Intravesical instillations of Bacillus Calmette-Guérin (BCG) with up to 3 years of maintenance therapy remain the current therapeutic gold standard for patients with high-risk nmiUCB [15]. Alternatives such as device-assisted intravesical chemotherapy, novel topical drug delivery systems, and systemic application of immune checkpoint inhibitors are currently being tested, although results with longer follow-up are pending [15]. Overall, according to current European Urology Association guidelines, RC is recommended for patients with nmiUCB in BCG-unresponsive tumors and initially for "Very High Risk (VHR)" tumors [15]. Seven clinical prognostic factors (tumor stage, World Health Organization (WHO) 1973 grade, WHO 2004/2016 grade, concomitant Carcinoma-in-situ, number of tumors, tumor size, and age) are used to define this VHR group, since molecular markers studied so far, such as high tumor mutational burden or histological evidence of lymphovascular invasion in TURBT specimens, don't sufficiently predict secMI under conservative therapy [15]. In a bicentric study of RC in 521 MIBC patients (399 and 122 with primMI and secMI, respectively) by our group, we evaluated the impact of European

Table 1. Brief summary of current data (chronological order) analyzing prognostic differences between primary and secondary muscle invasion in patients with bladder cancer concerning cancer-specific mortality following radical cystectomy.

Study	Design	Sample size (portion of secMI)	Male sex	FU after RC (mos)	CSM after RC*;#
[2]	R, UC	55 (12, 22%)	NA	49–55	10-yrs: 53 (secMI) vs. 52% (primMI), p=NS
[3]	R, UC	239 (70, 29%)	182 (76%)	33–40	HR* 0.82 (95%-CI, 0.47–1.43), p=.480
[4]	R, UC	188 (54, 29%)	144 (77%)	41	HR* 0.97 (95%-CI, 0.55–1.71), p=.900
[5]	R, MC	1150 (365, 32%)	914 (80%)	NA	HR* 0.60 (95%-CI, 0.47–0.80), p<.001
[6]	R, UC	150 (25, 17%)	121 (81%)	46	HR# 0.77 (95%-CI, 0.34–1.72), p=.524
[7]	R, UC	671 (190, 28%)	512 (76%)	NA	HR* 2.38 (95%-CI, 1.60–3.54), p<.001
[8]	P, MC	521 (122, 23%)	388 (74%)	65	HR# 0.93 (95%-CI, 0.68–1.27), p=.637
[9]	R, UC	768 (293, 38%)	569 (74%)	109	HR* 1.42 (95%-CI, 1.07–1.89), p=.010
[10]	R, UC+	288 (43, 15%)	215 (75%)	48	HR* 1.78 (95%-CI, 0.99–3.20), p=.054
[11]	R, RD	1036 (333, 32%)	NA	NA	HR* 1.09 (95%-CI, 0.91–1.30), p=.NS
[12]	R, MC	572 (168, 29%)	445 (78%)	37	5–yrs: 53.5 (secMI) vs. 35.5% (primMI), p<.001
[13]	R, UC+	333 (48, 14%)	52 (16%)	29–31	HR* 1.33 (95%-CI, 0.71–2.49), p=.NS
[1]	R, RD	556 (50, 9%)	NA	42	HR* 0.93 (95%-CI, 0.57–1.53), p=.780

Legend: CSM: cancer-specific mortality; CI: confidence interval; FU: follow-up in months; HR: hazard ratio; MC: multicentre; mos: months; NA: not available; NS: not significant; P: prospective study; R: retrospective study; RC: radical cystectomy; RD: registry data; secMI: secondary muscle-invasion; UC: unicentre; yrs: years; *multivariate Cox model with primary muscle invasion as reference; #univariate CSM rate with primary muscle invasion as reference; +all patients received neoadjuvant chemotherapy before RC.

Organisation for Research and Treatment of Cancer (EORTC) risk groups at the time of nmiUCB on CSM after RC (Table 1) [8]. Of 122 patients (23.4%) with secMI in this cohort, 44 were stratified to the EORTC high risk group B (14–23 points) based on findings of any TURBT while 30 were stratified to high risk group B based on findings of their last TURBT still verifying nmiUCB. Both patient subsets were found to have a significantly higher CSM following RC for progression to secMI compared to patients undergoing RC for primMI (HR 1.27, $p = .032$ and HR 1.19, $p = .041$, respectively) [8].

From our point of view, two important conclusions can thus be drawn from the available evidence: (1) conservative therapies for patients with primary cT1 UCB and secMI are associated with a prognostic deterioration compared to early RC for non-muscle invasive (nmi) clinical tumor stages, and (2) no fully reliable parameters exist for predicting secondary muscle invasion with conservative therapy for patients with primary nmUCB. In summary, the important results reported by Møller et al. once again underline the need for an improved stratification of patients with high-risk nmiUCB based on progression risk, as secMI under conservative treatment strategies is associated with an even worse prognosis compared to primMI for a considerable proportion of patients. At least in these patients, RC is currently performed too late.

Headline

What's still going wrong in bladder cancer treatment?

Acknowledgment

No funding was obtained for this letter.

Disclosure statement

No potential conflict of interest was reported by the author(s). No author has direct or indirect commercial financial incentives associated with the publication of this article.

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Received 24 May 2022; revised 11 July 2022; accepted 22 July 2022