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REVIEW ARTICLE

Clinical markers of morbidity, mortality and survival in bladder cancer patients treated with radical cystectomy. A systematic review

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ABSTRACT

Context: Radical cystectomy and pelvic lymph node dissection (RC and PLND) are an essential part of the treatment paradigm in high risk bladder cancer. However, these patients have high rates of morbidity and mortality related both to the treatment and to the disease.

Objective: To provide overview of current literature about clinical markers that can be used to predict and improve BC-patient outcomes at the time of RC and PLND and to study if they are properly validated.

Evidence acquisition: A systematic literature search was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria between January 1990 and October 2018 to identify English written original and review articles relevant to this topic. Prospective and retrospective studies were included.

Evidence synthesis: There are several risk factors identified from non-randomised trials that can be improved before surgery to reduce perioperative mortality and morbidity. These include poor nutritional status, anaemia, renal function and smoking. Preoperative nomograms have also been developed to help decision-making and to inform patients about the risks of surgery. They can be used to estimate risk of postoperative mortality after RC and PLND with accuracy varying from 70 to 86%. These nomograms are largely based on retrospective data. Likewise, nomograms developed to calculate estimates about patient's overall and cancer specific survival have the same limitations.

Conclusion: Clinical markers to predict morbidity, mortality and survival in patients with bladder cancer treated with RC and PLND may help to improve patient outcomes and treatment decision-making, but available data come from small retrospective trials and have not been properly validated. Prospective, multi-centre studies are needed to implement and disseminate predictive clinical markers and nomograms such that they can be utilised in treatment decision-making in daily practice.

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1. Introduction

Bladder cancer (BC) is the 9th most common cancer in worldwide and more than 330,000 new cases are diagnosed every year with more than 30,000 yearly cancer deaths [1]. At the time of diagnosis, approximately 30% of patients have muscle invasive bladder cancer (MIBC) and if left untreated, MIBC leads to death within 2 years of the diagnosis in >85% of patients [2]. Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the gold standard of treating MIBC [3]. In addition to surgery, neoadjuvant chemotherapy (NAC) is recommended for patients who are fit for cisplatin-based chemotherapy [4]. RC is also an option in treating high risk NMIBC, especially in BCG failure.

Although RC is considered major surgery and NAC exposes patients to severe adverse events, both morbidity and mortality of RC have significantly decreased over the past years. In a recent retrospective study from Finland covering 1385 RCs between years 2005 and 2014, RC related mortality was only 4.4%. In addition, the study demonstrated that the use of NAC was not associated with increased morbidity nor mortality [5]. It has also been demonstrated that functional and oncological outcomes can be improved in high-volume centres with at least 40–50 RCs per year operated by high-volume surgeons and an experienced team [6]. Although there is a decrease in RC related morbidity and mortality, RC still entails significant risk of peri- and postoperative complications with rates of 50–64% within the first 90 days after surgery [7,8]. Although there are several studies of biomarkers predictive of surgical and oncological outcome after RC, few are used in clinical practice. In this systematic review we summarise the literature about clinical findings and predictors associated with morbidity, mortality and survival in BC patients treated with RC and PLND. The aim is to identify clinical markers that can be used in treatment decision-making, in order to improve patient outcomes and in preoperative patient counselling. Properly validated markers could be used not just in urological but also in other patient populations.

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2. Evidence acquisition

A literature review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) criteria and the process of identifying references is presented in Figure 1 [9].

Medline, Embase and Scopus database search of the English literature was performed between January 1990 and October 2018. Search terms were: 'bladder cancer' AND 'radical cystectomy' AND 'morbidity', 'bladder cancer' AND 'radical cystectomy' AND 'complication', and 'bladder cancer' AND 'radical cystectomy' AND 'survival'. Articles of interest and review articles were surveyed and verified for any missed reports. Prospective and retrospective studies were included. The final literature review and selection was overseen and approved by all authors.

3. Evidence synthesis

3.1. Markers for surgical morbidity and mortality after radical cystectomy

3.1.1. Preoperative nutritional status

The most common variables to assess preoperative nutritional status in previous studies have been weight loss before the operation, low body-mass index (BMI) and low serum albumin level. Different cut-off values have been used in different studies, but BMI $<18 kg/m^2$, serum albumin <3.5 g/dl, and weight loss $>5\%$ within 3 months or $>10\%$ within 6 months are the most commonly used parameters. Overall nutritional deficiency is relatively common in RC patients and it seems to be associated with increased 90 d morbidity, mortality and decreased long-term survival [10,11]. This may reflect the effect of invasive cancer on the metabolism, but also that BC patients are typically elderly with unfavourable risk factors including smoking and sedentary life-styles. Although obese patients (BMI $\geq 30 kg/m^2$) may have higher short-term complication rates, their overall survival rates seem to be comparable to non-obese patients [12]. In previous studies low serum albumin levels preoperatively have been associated with perioperative complications, poorer cancer specific survival (CSS), relapse free survival (RFS) and overall survival (OAS) after RC and PLND [11,13–15]. However, all this data come from retrospective trials and no prospective studies with validation of the results are available. In addition, there are no prospective randomised studies to assess the effect of preoperative nutritional intervention to these endpoints.

3.1.2. Muscle mass status and sarcopenia

Several retrospective trials have demonstrated that low muscle mass (sarcopenia) is associated with increased risk of complications and poorer outcome after RC and PLND [16–20]. However, definitions and cut-off values vary between the studies. This parameter is relatively straightforward to measure from CT-scans but requires some expertise and computer software to provide accurate measurements.

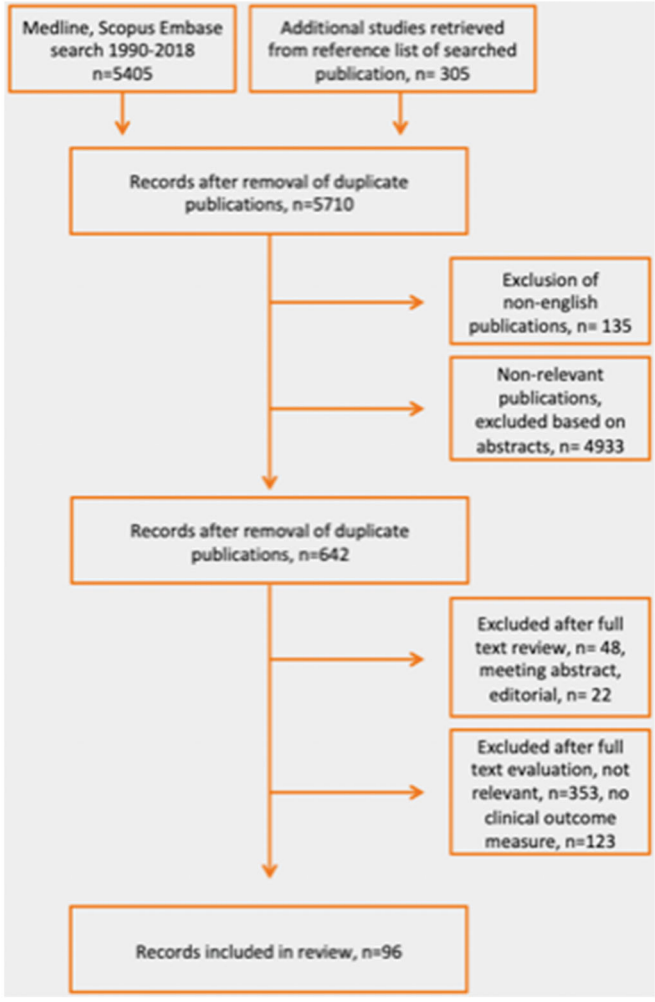

Figure 1. Evidence acquisition flow-chart.

The most common parameter is psoas muscle mass which has been shown to be associated with complications and poorer survival after RC and PLND [18,19]. In a recent relatively large retrospective study with 500 patients undergoing radical cystectomy, sarcopenia was a comorbidity-independent predictor of poorer 5-year OAS and CSS compared to patients without sarcopenia [21]. Low psoas muscle mass was also shown to predict poorer survival in patients who received NAC before radical surgery [22]. Patients who consume oral nutrition and multivitamin supplement perioperatively have reduced prevalence of sarcopenia and this seems to be beneficial at least in light of fewer and less severe complications following RC [23]. There is still lack of validated data and series have been done in a relatively low number of patients. Large blinded studies are needed to determine whether oral nutritional supplement interventions can improve outcomes following RC.

3.1.3. Preoperative anaemia and perioperative transfusions

Perioperative blood transfusion has been inconsistently associated with adverse outcomes during cancer surgery. BC patients especially are at increased risk of anaemia because they often present haematuria preoperatively. In addition,

the use of NAC may cause decreased bone marrow function leading to anaemia.

Some studies have reported increased risk of complications (especially infectious) in transfused patients undergoing RC and PLND [24–27]. Perioperative anaemia has been associated with predicted poor CSS and OAS, and it is also related to adverse histopathological characteristics and might even give additional prognostic information in patients undergoing RC and PLND [28,29]. Similarly, to above mentioned factors, no prospective data exists.

3.1.4. Nomograms and calculators to predict complications and postoperative mortality after RC and PLND

Accurate nomograms predicting complications and postoperative mortality could be of value when treatment options are discussed with patients. Especially important they could be when RC and PLND are considered as a treatment option in elderly patient populations and patients with co-morbidities. Few nomograms to predict mortality after RC and PLND are available, and only two of them have been validated in external cohorts [30–36]. These nomograms and their available validation studies are summarised in Table 1. ISBARN, AZIZ and MORGAN-nomograms can be used to predict 90d mortality after RC and PLND, whereas the modified POSPOM-nomogram can predict 30d mortality [30,31,34,36]. With the modified POSPOM-nomogram, derived from a large French cohort of over 5,000,000 patients, in-hospital mortality after surgery can be predicted [35,36]. All these nomograms have been developed using retrospective data from both single and multicentre cohorts. In the original trials their accuracy to predict postoperative mortality varied between 70% and 86% [30,31,34,36]. ISBARN and AZIZ-nomograms are externally validated and in these trials the accuracy was between 67% and 71%, respectively [31–33].

3.2. Markers of survival and prognosis after radical cystectomy

3.2.1. Extent of pelvic lymph node dissection

PLND is one of the important steps during radical BC surgery. Extent of dissection can be roughly divided as follows: limited – obturator fossa, standard – up to the ureteric crossing of iliac vessels, extended – up to the aortic bifurcation. However, there is no consensus what is the optimal PLND template, how many LNs should be removed and what is the best technique to perform this procedure. In addition, the comparability of the results from different studies is difficult since definition of PLND-templates vary between the cohorts.

Since the year 2000 there is several studies that have suggested that meticulous PLND is an important factor in determining patient survival after RC and PLND and limiting PLND to only region near to obturator fossa (standard PLND) will miss many LN metastases [37–46]. On the other hand, one study concluded that the majority of node positive patients have node disease in the limited or standard template and only a minority of patients have metastasis in the extended template if the limited template is clear of metastasis [47]. Also, the use of NAC may diminish the need for extended PLND during RC [48]. In a recent prospective randomised trial extended PLND failed to show a significant advantage over limited PLND in RFS, CSS, and OAS [49]. However, the inclusion of T1G3 patients to this study may contribute to the negative result.

There is a recent meta-analysis about the effect of extended PLND to the RFS in patients after RC and PLND [50]. In 11 studies analysed, the trend was clear that the extended LND reveals more LN metastases compared to the standard PLND (odds ratio = 1.39; 95% CI: 0.96–2.00; $p = 0.08$). Patients with extended PLND gained survival benefit [the overall odds ratio for the 5-year RFS 1.63 (95% CI: 1.28–2.07, $p < 0.001$)] and complication rate and perioperative mortality were equal to the standard PLND group. Another meta-analysis reported OS, CSS and RFS after RC and PLND from several studies [51]. Comparing the groups with the most extensive PLND to those with the least extensive, patients with the most extensive PLND had 28%, 34% and 36% reduced risks, corresponding to OAS (summary related risk estimate (SRRE) = 0.72; 95% CI, 0.64–0.80), CSS (SRRE = 0.66; 95% CI, 0.54–0.80) and RFS (SRRE = 0.64; 95% CI, 0.50–0.82), respectively.

3.2.2. Extranodal extension and lymph node density

In patients presenting LN metastasis at the time of surgery, extranodal extension (ENE) and lymph node density (LND) are both related to poor survival. ENE, defined as extracapsular extension of cancer in a metastatic LN, is an independent risk factor of RFS after RC and PLND [52]. In a large retrospective cohort of 748 patients, ENE was also an independent predictor of CSS [53]. In the same study, adding ENE to a multivariable model including pathologic T stage, tumour grade, age, gender, lymphovascular invasion (LVI), surgical margin status, LND, number of LNs removed, number of positive LNs, and adjuvant chemotherapy improved predictive accuracy for RFS and CSS from 70.3% to 77.8% ($p < 0.001$) and from 71.8% to 77.8% ($p = 0.007$), respectively.

LND is defined as proportion of metastatic LNs from total count of LNs removed. LND is not only a representation of tumour burden or the extent of PLND, it also reflects the natural variation in the total number of pelvic LNs between different patients and the meticulousness of a pathologist to detect LNs from the templates [54].

Different cut-off levels have been used in previous studies, but it has been suggested that the prognostic value of LND should be seen as a continuum of risk and LND <6% represents the best possible outcome in patients with nodal disease [55–60]. Most of these studies have shown that patients with lower LND have better DSS even in multivariate models and after adjuvant chemotherapy. However, in one study LND (cut-off of 20%) had a significant impact on survival in univariate model, but not in the multivariate model [52]. All of these studies have been done without NAC and they are retrospective in nature. There is still need of validation of the

Table 1. Nomograms and validation studies to predict complications and postoperative mortality after radical cystectomy.

Nomogram	Variables	End point	Study type	Patients	Accuracy	Validations	Accuracy in validation study
ISBARN [30]	Age, stage, grade, histological subtype	90 d mortality after RC and PLND	Retrospective, multicentre, SEER database	10981 (5471 in external validation cohort)	70%	Aziz et al. [31] Taylor et al. [32] D'Elia et al. [33]	69% [31], 69% [32], 67% [33]
AZIZ [31]	Age, ASA score, hospital volume, pN, pM	90 d mortality after RC and PLND	Retrospective, multicentre	597	79%	D'Elia et al. [33]	71%
MORGAN [34]	Age, clinical stage, CCI, serum albumin	90 d mortality after RC and PLND in patients ≥75 years	Retrospective, single centre	220	75%	N/A	N/A
POSPOM (modified) [36]	Age, comorbidities, major urologic surgery	30 d mortality after RC and PLND	Retrospective, single centre	1083	86%	N/A	N/A

RC: radical cystectomy; PLND: pelvic lymph node dissection; SEER: surveillance, epidemiology and end-results program; ASA: American society of anaesthesiologists; pN: pathologic lymph node stage; pM: pathologic metastasis stage; CCI: Chalson comorbidity index; POSPOM: preoperative score to predict postoperative mortality; N/A: not applicable.

results in prospective studies with predefined PLND templates and standardised histopathological reporting.

3.2.3. Lymphovascular invasion

Lymphovascular invasion (LVI) has been documented to be a poor prognostic factor in several solid organ tumours including patients with upper urinary tract carcinoma and urothelial carcinoma in TURBT [61,62]. Patients having LVI present in their TURBT specimen are at risk of worse OAS, LN-positive disease and pathologic upstaging after RC [63]. In addition, in patients without LN metastasis at the time of RC and PLND, LVI has also been demonstrated to be a prognostic factor of survival. It may be even as important as lymph node involvement as a prognostic factor for these patients [64]. In the largest international retrospective cohort, LVI improved the predictive accuracy of the standard predictors for recurrence (hazard ratio 1.68, $p < 0.001$; $+2.3\%$) and CSS (1.70, $p < 0.001$; $+2.4\%$) in patients without LN metastasis [65]. By contrast, it only marginally improved the prediction of outcomes in patients with LN metastasis. In one retrospective study of 958 patients LVI was an independent predictor of recurrence and decreased CSS and OAS in node negative patients, but again, not in patients with LN metastases [66]. In another, also retrospective, study of 2005 patients, 10 years RFS in patients without LVI was 74% compared with 42% in those with LVI ($p < 0.0001$). Similarly, 10 years OAS was 43% in patients without LVI compared with 18% in those with LVI ($p < 0.0001$)[67]. The same trend was also seen in a smaller retrospective cohort of 356 patients with mean follow-up of 45.6 months; patients with LVI had higher pathological stage (74% had pT3 or pT4 disease) compared to those without LVI [68]. In one study LVI was a prognostic factor of poor survival in univariate analysis, but on multivariate analysis pathologic T-stage was the only significant prognostic factor in the LN negative group [69].

The role of LVI as a marker of poor prognosis was also the finding in the recent meta-analysis, but still there are no prospective studies to validate these results [70]. If validated, this data might become useful in clinical practice for selecting which patients would benefit from neoadjuvant as well as adjuvant therapies.

3.2.4. Nomograms and calculators to predict advanced disease, recurrence and survival in patients treated with RC and PLND

Multivariate nomograms are developed to give more accurate and relevant individualised prediction of survival after cystectomy and thereby improving patient counselling and treatment selection. They are summarised together with their validation studies in Table 2 [71–82]. Two of them are used in pre-cystectomy and four in post-cystectomy settings.

Pre-cystectomy nomograms are used to assess the risk of advanced disease at the time of surgery and to give a preoperative estimate about individual patient's CSS if surgery is performed [71,73]. The two nomograms are based on retrospective multicentre data and only the nomogram developed by Karakiewich et al. is externally validated and its accuracy

Table 2. Nomograms and validation studies to predict advanced disease, recurrence and survival in patients treated with radical cystectomy.

Nomogram	Phase	Study type	Patients	Variables	Endpoint	Accuracy	Validation studies	Accuracy in validation study
Karakiewicz 1 [71]	Precystectomy	Retrospective, multicentre	726	T-stage, WHO grade, CIS, age, gender, NAC	Risk of having advanced disease (T3–4 or N+) at RC and PLND	76% (pT3–4) and 63% (pN1–3)	Ku et al. [72]	59% (pN+)
Di Trapani [73]	Precystectomy	Retrospective, multicentre	423	TURBT-stage, ASA-score, gender, age, NAC	CSS	67%	N/A	N/A
IBCNC [74]	Postcystectomy	Retrospective, multicentre	9064	Age, gender, time from dg to RC, pT, grade, histologic subtype, regional LN status	RFS	75%	Zaak et al. [75]	86%
BCRC [76]	Postcystectomy	Retrospective, multicentre	731	Age, gender, pT, grade, CIS, LVI, pN, NAC, ACT, ART	CSS and OAS	79% CSS and 73% OAS	Brooks et al. [77], Nuhn et al. [78], Zaak et al. [75], Moon et al. [79]	5 years CSS 84% [77], 73% [78], 85% [75], 76% [79] and 5 years OAS 82% [77], 69% [78], 78% [75], 76% [79]
Karakiewicz 2 [80]	Postcystectomy	Retrospective, multicentre	731	Age, gender, pT, grade, CIS, LVI, pN, NAC, ACT, ART	RFS	78%	Brooks et al. [77], Nuhn et al. [78], Zaak et al. [75]	5 years RFS 81% [65], 75% [66], 84% [64]
Simone [81]	Postcystectomy	Retrospective, single centre	818	Age, gender, pT,pN, LVI, CIS, STSM, LNDe, extent of PLND	DFS and CSS	5 years DFS 80% and 5 years CSS 80%	Validated as part of original study	5 years DFS 82% (Europe), 72% (Africa), 74% (North America) and 5 years CSS 85% (Europe), 74% (Africa), 76% (North America)
Williams [82]	Postcystectomy	Retrospective, SEER and TCR-medicare cohorts	5325	NAC, PLND, age, marital status, sex, T-stage, hydronephrosis, grade, CCI	CSS and OAS	3- and 5 years OAS 65 % and CSS 66%	Validated as part of original study	Prospective validation under investigation

T: tumour stage, WHO: World health organization, CIS: carcinoma *in situ*, NAC: neoadjuvant chemotherapy, N: nodal stage, TURBT: tranurethral resection of bladder tumour, ASA: American society of anaesthesiologists, CSS: cancer spesific survival, N/A: non-applicable, RC: radical cystectomy.
LN: lymph node, RFS: recurrence-free survival, LVI: lymphovascular invasion, ACT: adjuvant chemotherapy, ART: adjuvant radiotherapy, OAS: overall survival, STSM: soft tissue surgical margin, LNDe: lymph node density, DFS: disease free survival, PLND: pelvic lymph node dissection.
CCI: Charlson Comorbidity Index, SEER: Surveillance, Epidemiology, and End Results database, TCR: Texas cancer registry database.

Table 3. Summary of studies using neutrophil-to-lymphocyte (NLR) ratio to predict survival, progression, advanced disease and response to preoperative chemotherapy in patients undergoing radical cystectomy.

Study	Patients	NLR cut-off value	Objective of study	Key findings
Hermans et al. [84]	424	3.0	5 years CSS	Better prognosis in patients with lower NLR (57% vs. 75%) in uni- and multivariate analysis
Bhindi et al. [85]	418	2.9	RFS, CSS and OAS	Among complete blood count-based biomarkers NLR most efficient predicting RFS, whereas NLR and haemoglobin most efficient predicting CSS and OS
Gondo et al. [86]	189	2.5	1, 3 and 5 years CSS	NLR independent prognostic factor for survival
Krane et al. [87]	68	2.5	OAS, CSS and extravesical disease	NLR and hypoalbuminaemia independent predictors of survival and extravesical disease
Viers et al. [88]	899	2.7	RFS, CSS and OAS. Extravesical disease, LN involvement	Elevated NLR associated with advanced disease, recurrence and cancer-specific and all cause mortality
D'Andrea at al. [89]	4335	2.7	RFS, CSS and OAS	NLR independet predictor of RFS, CSS and OAS on multivariate analysis. Also improved prediction of extravesical disease
Kang et al. [90]	385	2.5	CSS and OAS	NLR associated with advanced disease and poorer 5 years survival estimates up to 2 years after surgery
van Kessel et al. [91]	123	2.7	PFS and OAS, response to NAC	NLR correlated with unresponsiveness to NAC and poorer PFS and OAS, but differences were not statistically significant
Buisan et al. [92]	205	2.26	outcomes to NAC, PFS, CSS and OAS	75 pts recieved NAC and NLR correlated with pathologic response, PFS, CSS and OAS
Morizawa et al. [93]	110	2.6	RFS, CSS and OAS	Increase in the NLR during follow up after RC potential marker for the early detection of recurrence before radiological detection
Lucca et al. [94]	4061	2.7	OAS and CSS	Meta-analysis from 5 different studies; preoperative NLR associated with advanced stage, LN metastasis and worse prognosis

CSS: cancer specific survival, RFS: recurrence free survival, OAS: overall survival, LN: lymph node, NAC: neoadjuvant chemotherapy.

to predict locally advanced disease or LN metastases was 76% and 63% in the original trial and 59% to predict LN metastases in the validation trial, respectively [71,72].

Post-cystectomy nomograms predict patient's risk of recurrence and survival relying on the data derived from the post-cystectomy pathology [74,76,80–82]. They may be useful in assessing patient's need of adjuvant therapies and in the development of better follow-up protocols. All these nomograms consider patient's age, gender and post-cystectomy pathology, but other variables may differ. In the nomograms predicting RFS the accuracy varies between 75% to 80% and in the nomograms predicting CSS between 66% to 80%, respectively [74,76,80–82]. In the validation trials the accuracy to predict RFS and OAS varies from 66% to 86% between different nomograms and study populations [75,77–79,81,82]. Nomograms developed by Simone et al. [81] and Williams et al. [82] were externally validated as part of the original study.

3.2.5. Neutrophil-to-lymphocyte ratio

As presented above, the traditional way to predict patient's prognosis relies on factors such as pathological tumour stage, grade and lymph node involvement. Until recently, several systemic inflammatory response (SIR)-related factors have been studied as markers of adverse events and survival in patients undergoing RC. Of these SIRs, neutrophil-lymphocyte ratio (NLR) is one of the most promising [83]. NLR is inexpensive, reproducible, easily available and calculated from the peripheral blood components. NLR cut-off values differ in these studies from 2.26 to 3. These studies indicate that high NLR is related to the adverse outcomes in patients undergoing treatment for bladder cancer [84–94]. NLR has been related to poor prognosis, high-grade features of the tumour and risk of advanced disease at the time of RC [84,86,89,94–96]. It has also been related to the risk of recurrence and the risk of extravesical disease in patients undergoing RC [85,87,93,97]. High NLR also seems to indicate poor response to the NAC before surgery [91,92]. These studies and their key findings are summarised in Table 3.

3.3. Discussion

When MIBC or high risk NMIBC is detected in a TUR-BT specimen, it is a crucial moment for the patient who might is diagnosed with a life-threatening cancer. For the urologist this is also the appropriate moment to consider treatment options. The patient must be informed of the treatment options, how they are performed, what can be achieved by performing them, what is the expected prognosis after these major interventions, what are the possible side effects, how do they affect his or her quality of life, and what is the risk of mortality related to the interventions. Another challenge is that the time-period from diagnosis to definitive treatment should be as short as possible, and there is only limited time to improve patient related factors. Bladder cancer patients are often long-term smokers with compromised pulmonary function, burdened with vascular diseases, and their nutritional status may be sub-optimal. Every effort to optimise, nutritional status pulmonary and cardiovascular function prior to surgery (albeit smoking cessation and mild exercise) may be crucial to improving perioperative outcomes and patient survival.

Preoperative nutritional status is easily measured by detecting hypoalbuminaemia from the blood sample or sarcopenia from preoperative CT-scans [11,13,17]. These parameters are relatively poorly studied, and their importance may be underestimated in current clinical practice in many centres performing RC. However, by this strategy high-risk

patients could be relatively easily identified. Irrespective of measurements of nutritional status, it may be beneficial to give some nutritional advise to every patient preparing for RC since there is little risk to do harm to the patient with these interventions. Large blinded studies are needed to determine whether oral nutrition supplement interventions can improve outcomes following RC.

BC patients have quite often low haemoglobin levels at the time of RC, because they often have haematuria and the use of NAC also increases the risk of preoperative anaemia. Even though there are no randomised studies to investigate the benefit of preoperative correction of anaemia, it may be beneficial since data from retrospective studies suggest that perioperative anaemia is associated with poor prognosis [28].

As discussed before it would be of great benefit to have proper estimates about individual patients' risks and benefits preoperatively to guide treatment options in MIBC. To help this decision-making several preoperative nomograms have been developed [30,31,34,36]. The problem with every nomogram is that it should be properly validated to give reliable estimates. Without this process of validation it is not possible to give any general recommendations to use them outside selected populations.

PLND is a crucial part of radical surgery in BC, although it's extent can be debated. Although two meta-analysis showed benefit using more extended approach this was not the case in the prospective randomised setting [49–51]. ENE and LND are two important parameters that can be detected in the PLND specimen. These parameters are not often reported in pathology reports, but LND can be easily calculated if the number of metastatic lymph nodes and the total amount of removed lymph nodes are known. ENE has been associated with RFS and CSS whereas LND has been related to CSS in previous studies [52,53,55–59]. By giving this information they can be both utilised as prognostic variables in BC-patients after RC and PLND. When it comes to which technique should be used during the surgery open, robotic and laparoscopic approaches seem to give equivalent 5 years RFS, CSS and OS rates [98]. Also, at least in selected patients, nerve-spearing and prostate capsule-sparing cystectomy is an appropriate option with acceptable oncological and functional results [99].

Several nomograms have been developed to calculate estimates of individual patient's prognosis after radical cystectomy, two of these using pre-operative variables and four post-cystectomy variables [71,73,74,76,80–82]. They may be useful in the preoperative planning of surgery in terms of local control and extent of PLND and to estimate CSS after surgery. This information could be of great value to the patient and surgeon when discussing different treatment options. Nomograms that require information gathered during and after the surgery can be used to gain information about estimates of CSS, RFS and OAS [74,76,80–82]. These estimates can further be used to determine surveillance protocols and they may be useful when considering adjuvant treatment options. All these nomograms are based on retrospective data. Most of them used data from multiple institutions at the time of development, but their generalisability may be questioned since their accuracy varies in the validation studies.

Beyond the scope of this review are several biomarkers that may be used to predict patient outcome after BC surgery. None of them have yet gained wide acceptance in clinical use and they are all still investigational. From the blood measured variables only NLR was covered since it is inexpensive, reproducible, and readily available to use in everyday practise. This relatively easy measurement of peripheral blood components is related to adverse outcomes in patients undergoing radical cystectomy and it can potentially be used to predict response to NAC as well as patient's survival after surgery [84–97].

4. Conclusions

There is still a need for prospective trials and validated data to gain better information and estimates to improve outcomes in this challenging patient group. To answer this need *The Nordic Urothelial Cancer Group* is launching a prospective, multi-institutional and international trial to collect data from patients undergoing RC for BC in the Nordic countries. The aim is to validate existing prediction tools and to discover novel ones for predicting morbidity related to RC, response to NAC and oncological outcomes.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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