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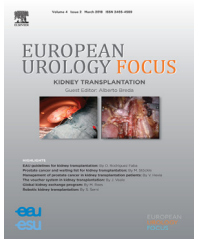

Review – Bladder Cancer

Predicting Response to Neoadjuvant Chemotherapy in Bladder Cancer

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A bstract

Context: Neoadjuvant chemotherapy (NAC) is recommended prior to radical cystectomy in the setting of muscle-invasive bladder cancer. Despite a 5–10% survival benefit, some patients do not respond to NAC. Identification of the nonresponders could avoid side effects and delay in surgery.
Objective: The objective of this review is to summarize the latest evidence regarding predictors of NAC response.
Evidence acquisition: MEDLINE, Embase, and the Cochrane Library databases were searched for published studies including clinical, pathological, molecular, and imaging tests or factors that can be applied before or during NAC to predict its results.
Evidence synthesis: Patient characteristics and imaging techniques seem to have minimal utility to predict NAC response. Only advanced magnetic resonance imaging techniques seem to have a potential role. There is insufficient evidence to suggest a change in NAC paradigm for variant histology, whereas the most promising results come from molecular characterization of tumors.
Conclusions: No validated instrument currently exists to predict NAC response. While awaiting further evidence, no strong recommendation can be made toward a shift in paradigm.
Patient summary: The most effective and aggressive treatment for muscle-invasive bladder cancer is radical cystectomy preceded by effective neoadjuvant chemotherapy. In this paper, we reviewed the current literature and published evidence to identify predictors of response to neoadjuvant chemotherapy for muscle-invasive bladder cancer. To date, no instrument exists to predict which patients will respond to neoadjuvant chemotherapy.

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1. Introduction

Radical cystectomy (RC) with pelvic node dissection remains the most effective treatment for muscle-invasive bladder cancer (MIBC). Recent literature demonstrates a 5–10% increase in cancer-specific survival (CSS) when neoadjuvant chemotherapy (NAC) is utilized for cT2–4, N0, M0 disease [1]. NAC has the potential to lower the burden of micrometastasis at surgical treatment. However, a percentage of patients fail to respond to NAC and may experience a potentially fatal delay of surgery, while incurring the toxicity of treatment. More accurate stratification of

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patients undergoing NAC is necessary to identify patients more likely to respond and to shift toward other strategies in patients likely to fail. Current evidence supports only the use of cisplatin-based regimens in neoadjuvant setting; however, we are on the horizon of seeing multiple novel neoadjuvant treatment regimens [1].

2. Evidence acquisition

In this study, we aim to review current predictors of response to NAC; the tests or factors that can be utilized before the treatment to determine the patients who would benefit most from NAC were evaluated. The definition of response to treatment is heterogeneous in literature; therefore, we chose to maintain wide inclusion criteria in order to capture studies evaluating the impact of cisplatin-based NAC regimens on pathological response, radiological response, and indirect criteria such as progression-free survival (PFS), CSS, and overall survival (OS). MEDLINE, Embase, and the Cochrane Library databases were searched for papers including any of the aforementioned criteria.

3. Evidence synthesis

3.1. Clinical factors

3.1.1. Disease-related factors

Retrospectively analyzing patients undergoing RC without NAC, Culp et al [2] found that patients considered to be at high risk experienced worse OS and CSS, thus hypothesizing that this subgroup of patients would benefit most from NAC. It should be noted, however, that preoperative classification was often not confirmed by final pathology, where 26.5% of high-risk patients were reclassified as low-risk patients and 49.2% of low-risk patients were reclassified as high-risk patients. Lyon et al [3] identified 1025 low-risk and 906 high-risk patients, and found that low-risk patients treated with NAC had higher odds of downstaging (pT0: odds ratio [OR] 3.05, 95% confidence interval [CI] 1.89–4.93, $p <$ 0.001; pT < 2: OR 2.53, 95% CI 1.64–3.89, <0.001) but without any significant increase in OS and CSS in comparison with those not undergoing NAC. Interestingly, 14% of low-risk patients treated with immediate RC were subsequently unable to receive adjuvant chemotherapy because of perioperative events rendering them ineligible for NAC.

MIBC guidelines recommend NAC if disease presents as at least stage T2 at diagnosis (primary) or develop from a non–muscle-invasive setting (secondary). Pietzak et al [4] retrospectively analyzed 245 primary and 43 secondary MIBC patients receiving cisplatin-based NAC, and on multivariate analysis, found that pathological response (OR 0.4; CI 0.18–0.84; $p = 0.02$), recurrence-free survival (RFS; $p = 0.007$), and OS ($p = 0.048$) were worse for secondary MIBC patients. The authors performed a genomic analysis and found significant differences between primary and secondary tumors, which will be described further in detail.

3.1.2. Patient-related factors

Smoking has been investigated as a component of resistance to cisplatin chemotherapy [5]. To date, only two studies have investigated the association between smoking and pathological response to NAC with conflicting results. In a cohort of 139 patients (T2-4a, N0, M0), Kim et al [6] found no association between smoking and complete pathological response ($p = 0.5$) or any response ($p = 0.2$). Additionally, odds of recurrence ($p = 0.6$) and cancer-specific death ($p = 0.9$) were not different between current, former, and never smokers. More recently, Boeri et al [7] found that current smokers were more likely nonresponders ($p = 0.007$) and that current smokers had a four times increased risk of nonresponse to NAC (OR 4.63; $p < 0.001$), and being a previous smoker increased the risk of nonresponse two times (OR 2.32; $p = 0.022$). The authors also demonstrated an association of the number of packs smoked per year with nonresponse (OR 1.04; $p = 0.029$) and RFS (hazard ratio [HR] 2.14; $p = 0.03$) in multivariate analysis.

Sarcopenia is associated with worse surgical outcomes [8]. Lyon et al [9] evaluated a cohort of 183 patients receiving cisplatin-based NAC before RC and defined sarcopenia through Skeletal Muscle Index; although the degree of change of subcutaneous fat was associated with downstaging in univariable analysis, this was not seen after multivariable adjustment ($p = 0.5$). These results are consistent with previous studies where no association was found between sarcopenia and NAC response [10,11].

3.2. Pathological factors

3.2.1. Pathological classification

The complexity of bladder cancer treatment is complicated by its histological heterogeneity. While most specimens reveal pure urothelial carcinoma, in up to 33% RC specimens, urothelial carcinoma demonstrated divergent differentiation that is commonly associated with high grade and advanced disease [12]. Urologists often have to decide whether to change standard treatment strategies in cases where divergent histology is found. Pure urothelial carcinoma is indeed associated with greater rates of pT0 at RC than mixed tumors [13].

3.2.1.1. Urothelial carcinoma with divergent differentiation. The definition of divergent differentiation refers to a tumor of urothelial origin in which any degree of “usual” urothelial carcinoma is mixed with a histological variant.

In a subgroup analysis from the randomized controlled trial (RCT) SWOG 8710, patients with mixed histology (squamous or glandular) were seen to have a survival benefit with NAC (HR 0.46; 95% CI 0.25–0.87; $p = 0.02$) compared with primary RC [14]. These results are consistent with the findings of Kaimakliotis et al [15] who reported similar oncological outcomes of NAC for patients with pure urothelial bladder cancer ($n = 54$) and variant histology ($n = 30$), with the latter being mostly represented by squamous or glandular differentiation. The presence of squamous or glandular variants was associated with higher rates

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of pathological downstaging (OR 4.01; 95% CI 1.16–13.9) but similar OS when compared with pure urothelial carcinomas [16].

Buisan et al [17] suggested that lower pre-NAC neutrophil-lymphocyte ratio (NLR) values were associated with improved response to NAC. They hypothesized that in patients with *squamous* differentiation of urothelial bladder cancer, NLR could have a prognostic role. Their findings demonstrated improved CSS ($p = 0.009$) for patients with NL < 5 treated with NAC when compared with upfront RC [18].

One of the most studied variant histologies is *micropapillary*. Results from various studies are summarized in a recent meta-analysis that investigated the effects of NAC in presence of micropapillary variant. Authors reported pathological complete response ranging from 11% to 55% without significantly affecting RFS (HR 1.23, 95% CI 0.52–2.93, $p = 0.6$), CSS (HR 0.9, 95% CI 0.48–1.7, $p = 0.8$), or OS (HR 1.35, 95% CI 0.98–1.86, $p = 0.1$) [19].

Plasmocytoid variant is a much rarer aggressive variant. Dayyani et al [20] described pathological downstaging after NAC in four of five patients with no benefit in outcomes. The largest cohort of patients with *plasmocytoid* variant ($n = 98$) has recently been described, and no specific subgroup analysis was performed for those receiving NAC. After adjusting for *plasmocytoid* in the multivariable analysis, this variant was associated with adverse pathological features, but no worse OS [21].

Sarcomatoid variant is an aggressive component of mixed tumors. The prognosis of these patients is generally poor, and data from the National Cancer Database suggests that aggressive treatment with RC is needed, but the role of multimodal therapy is uncertain [22]. Interestingly, it has been described that a higher amount of variant histology in RC specimens is seen after NAC than in transurethral resection of bladder tumor (TURBT) specimens; however, the percentage of variant histology on TURBT specimen was not associated with NAC pathological response. Similarly, mitotic proliferation was found to be lower after NAC, but pre-NAC mitotic rate was not a predictor of response [23]. A comprehensive analysis of different variants was performed with the data of 369 patients with different histological variants who received NAC. Authors found a significant benefit in OS with NAC compared with primary RC only for *neuroendocrine* variants (HR 0.49; 95% CI 0.33–0.74, $p = 0.001$) [24].

3.2.1.2. Nonurothelial carcinomas of the bladder. Here, we present a discussion on nonurothelial carcinoma; however, a detailed review is beyond the scope of this manuscript.

Pure squamous cell carcinoma is an aggressive disease known for its poor response to systemic therapy, which has been confirmed recently (HR 0.93, $p = 0.69$) [25].

Small cell carcinoma is an aggressive variant, frequently metastatic at presentation. Lynch et al [26] analyzed a heterogeneous cohort of patients with small cell carcinoma of the bladder, and their data suggest a higher rate of pathological downstaging at surgery (62% vs 9%) and improved long-term survival (median 159.5 vs 18.3 mo, $p < 0.001$) in small cell carcinoma patients receiving NAC.

Both *primary adenocarcinoma of the bladder* and *urachal carcinoma* have been shown to have no benefit with cisplatin-based chemotherapy [27].

Descriptions of other more rare variants are present in the form of case reports, and treatment strategies should be discussed in a multidisciplinary setting.

Owing to its retrospective nature, the reported literature is prone to bias that is furthermore increased by the lack of a pathological review of the sample in most of the studies. While awaiting further studies, in our opinion, there is not sufficient evidence to consider the presence of mixed histology as a contraindication to NAC. Different considerations should be made in the setting of pure nonurothelial tumors where multidisciplinary discussion is recommended.

3.2.2. Genomic alterations, expression, and biomarkers

Unlike malignancies such as lymphoma, targeted therapies for MIBC are not yet developed, but the natural history of the disease offers an adequate amount of tissue to be analyzed (before and after NAC/RC) in order to assess which cellular markers can predict the resistance to NAC and guide therapy.

As part of The Cancer Genome Atlas project (TCGA), analysis of MIBC samples revealed that bladder cancer carries one of the highest mutational loads, inferior only to lung cancer and melanoma. Recurrent mutations were found in 58 genes associated mainly with cell-cycle regulation, chromatin regulation, DNA repair, and canonical signaling pathways; interestingly, an association with early, clonal APOBEC cytidine deaminase mutations was found, and moreover several of the genomic alterations identified are potentially amenable to therapeutic targeting [28,29]. A quick review of cisplatin mechanism of action is needed to guide the discussion on genetic and molecular predictors of response, albeit detailed descriptions of molecular pathways are beyond the purpose of this review.

Cisplatin enters the cell through several membrane transporters, becomes activated, and causes DNA damage affecting cell survival and inducing apoptosis. There are indeed four mechanisms of cisplatin resistance that have been described: (1) pretarget resistance is intended as reduced intracellular accumulation (ie, CTR1) or intracellular sequestration of the drug; (2) on-target resistance is intended as the ability to repair or tolerate DNA damage, and it is mediated mainly by nucleotide excision repair proteins (ie, ERCC1), mismatch repair proteins and homologous recombination systems (ie, BRCA); (3) post-target resistance involves alterations of the signaling pathway that leads to apoptosis (ie, p53, BLC-2); and (4) off-target resistance occurs when signaling pathways not directly influenced by cisplatin are involved (ie, ERBB2/EGFR) [30].

3.2.2.1. Genomic alterations. According to the mechanisms of cisplatin resistance described, different studies evaluated the role of single or multiple genomic alterations, and a comprehensive summary can be found in Table 1. In particular, CTR1 expression significantly correlated with pathological downstaging or complete response following NAC in 47 patients ($p = 0.0076$)

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Table 1 – Summary of the main studies investigating genomic alterations.

Biomarker	Author	Main findings
Cell survival pathway		
P53	Qureshi [63]	No correlation
P53	Sarkis [64]	Overexpression associated with worse CSS
P53, mdm2	Kakehi [65]	Response to NAC related to p53 negative
P53	Stadler [66]	No correlation
P53	Plimack [67]	No correlation
Bcl-2	Cooke [68]	Overexpression associated with higher stages after NAC
P53, mdm2, Bcl-2	Maluf [69]	No correlation with downstaging, when combined correlation with survival
DNA damage repair		
BRCA-1	Font [70]	Low/intermediate expression associated with pathological response and longer survival
ATM/RB1/FANCC	Plimack [32]	Correlation with pathological response, PFS, and OS
ERCC2	Van Allen [34]	Mutated in responders
ERCC2	Liu [33]	Mutated in responders
ERCC2 and others	Iyer [71]	Loss of function mutation associated with response
ERCC1	Choueiri [72]	No significant association
FGFR3, ERBB2, PIK3Ca	Yang [35]	Mutations associated with response to NAC and better survival
Membrane transporters and others		
CTR1	Kilari [31]	Higher expression correlated with response
ERBB2	Groenendijk [73]	Missense mutations in complete responders

CSS = cancer-specific survival; NAC = neoadjuvant chemotherapy; OS = overall survival; PFS = progression-free survival.

[31]. The most interesting results come from the studies evaluating DNA damage repair (DDR) genes. A study from Plimack et al [32] reported a correlation between ATM/RB1/FANCC alterations and pathological response ($p < 0.001$), PFS ($p = 0.0085$), and OS ($p = 0.007$) both in AMAVAC- and in ddCG-treated patients. From the same cohort of patients, Liu and colleagues [33] looked for ERCC2 mutation and reported that mutations in this gene were associated with response to NAC (OR 8.3; 95% CI 1.4–91.4; $p = 0.01$). *ERCC2* is indeed a nucleotide excision repair gene initially investigated by Van Allen et al [34], which was found to be the only mutated gene enriched in 25 responders to NAC ($p < 0.001$). More recently, FGFR3, ERBB2, and PIK3Ca alterations were found to be associated with response to NAC ($p < 0.01$). In the survival analysis, patients expressing higher levels of FGFR3 had longer mean survival. Among the biomarkers, only strong expression of ERCC1 was associated with response to NAC ($p < 0.011$) [35]. Interestingly, in the aforementioned study by Pietzak et al [4], a separate genomic analysis showed that ERCC2 missense mutations were significantly enriched in patients with primary (17.1%) versus secondary MIBC (0%), hypothesizing a selection of cisplatin-resistant clones in secondary tumors potentially driven by bacillus Calmette–Guérin therapy.

Most of the findings presented in Table 1 are often derived from small cohorts and need further validation. However, ERCC2 and nucleotide excision repair genes play a key role in modulating the response to cisplatin and are to date the most validated single genes in predicting response to NAC. Currently, NCT02710734 and NCT03609216 are evaluating DDR mutational profile in a risk-adapted treatment of MIBC after NAC, including bladder-sparing approaches, and results will provide crucial information on the clinical impact of these mutations.

3.2.2.2. Gene expression profiling and molecular subtypes. The idea of profiling gene expression to analyze molecular activities in cancer cells was first developed in 2005. Authors identified 14 genes the expression of which was significantly different between responders and nonresponders to methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) NAC in order to create a numerical predictor scoring system [36,37] that was then extended to CG regimens [38]. Recently, these prediction scores were tested in the setting of a clinical trial of T2–4N0 patients, where patients were allocated to MVAC or carboplatin plus gemcitabine (CaG) NAC plus RC, upfront RC, or radiation therapy based on prediction scores and preferences. The positive predictive value for MVAC score was 85.7% (6/7); no patients received MVAC with a negative score. The positive and negative predictive values for CaG were 88.9% (16/18) and 33.3% (1/3), respectively [39]. Apart from the small sample size, one of the major limitations of these studies was the downstaging criteria used, which utilized only imaging for evaluation in some patients.

Based on RNA expression profiling, several groups have independently identified molecular subtypes of bladder cancer; although classifications exist, there is agreement about division in basal/squamous or luminal subtypes. The first are characterized by squamous features, markers of carcinoma in situ, and epithelial to mesenchymal transition, and are present at higher stages. Luminal tumors are instead associated with papillary features and development from non-MIBC (FGFR3 mutations) [40]. A recent consensus identified a set of six molecular subtypes, namely, luminal papillary, luminal nonspecified, luminal unstable, stroma rich, basal squamous, and neuroendocrine like. When focusing on NAC-treated patients, the comparison of survival between those receiving NAC and those not receiving

NAC suggested that patients with basal-squamous or luminal nonspecified tumors may benefit from NAC, while patients with a stroma-rich tumor may not [41].

When applying molecular classification to NAC, some studies are worth mentioning; Choi et al [42] focused on a cohort of 73 patients with MIBC at TURBT and identified three subtypes: basal tumors had good response to NAC despite the aggressiveness, luminal tumors had a better prognosis, while patients with p53-like subtype (p53 wild-type expression) were nonresponders to NAC (0/7). Interestingly, this subtype was found to be increased in RC specimens of NAC-resistant tumors. The group further studied these subtypes in the setting of a randomized trial including 60 patients treated with ddMVAC plus bevacizumab before RC. They confirmed the chemoresistance of p53-like tumors (5-yr OS 91% for basal type, 73% for luminal type, and 36% for p-53 like; $p = 0.015$), with a shift toward p53-like subtypes in RC specimens after NAC treatment [43].

More recently, a single sample genomic subtyping classifier integrating the previously described basal, with a subset defined claudin-low subtype [44], and luminal subtypes (the latter with further differentiation into infiltrated and noninfiltrated subtypes) was developed and tested on a multi-institutional cohort of 223 patients treated with NAC and a validation cohort of 82 patients. Luminal tumors had the best prognosis despite the treatment received; on the contrary, basal tumors had a worse prognosis when not treated with NAC. The prognosis for luminal-infiltrated tumors worsened despite the treatment with NAC. Claudin-low subtype demonstrated the worst prognosis irrespective of treatment strategies. No direct relationship between subtypes and pathological response was found with this model [45].

Interesting evidence supports the association between molecular subtypes and NAC. In particular, some subtypes with the characteristics of p53-like or claudin-low subtype have the worst prognosis despite NAC, indicating the need for new therapies in these subtypes. Immunohistochemical markers such as GATA3, uroplakin, and HER2 for luminal tumors and KRT5/6, KRT14, and p63 for basal tumors have been proposed to identify these subtypes; in particular, GATA3 and basal KRT5/6 were found to be sufficient to identify the molecular subtypes of bladder cancer with over 90% accuracy [40].

3.2.2.3. Tumor markers. Cellular adhesion molecules such as CEA and carbohydrate antigens such as CA 19-9 have a diagnostic and prognostic role in different tumor settings. Bazargani et al [46] measured the levels of CA-125, CA 19-9, and CEA prior to neoadjuvant therapy and after completion of the NAC (CG, ddMVAC, or combined treatment) and found that any pre-RC elevation of tumor markers was associated with worse 2-yr RFS ($p < 0.001$) and OS ($p = 0.009$). When analyzed individually, both CA 19-9 and CA125 maintained the associations, while CEA was not significantly associated with worse RFS or OS. Furthermore, tumor marker normalization prior to cystectomy was associated with longer time to progression ($p = 0.015$) and improved survival ($p = 0.037$).

Circulating tumor DNA (ctDNA) is being also evaluated as a biomarker for disease staging and progression. Christensen et al [47] evaluated the role of its dynamics during NAC as a predictor of response in 68 patients undergoing NAC and RC for MIBC. They reported that the presence of ctDNA before NAC was significantly associated with worse clinical outcomes after NAC and RC ($p = 0.001$). Similarly, the presence of ctDNA after NAC but before RC was associated with increased 12-mo and overall recurrence compared with the absence of ctDNA ($p < 0.001$), and all pT0 patients were ctDNA negative. Interestingly, 35/41 (85%) patients without detectable ctDNA before NAC experienced pathological downstaging and 9/17 (53%) patients with ctDNA clearance after NAC experienced pathological downstaging compared with none of those with persistent DNA.

3.2.2.4. Checkpoint inhibitors and future directions. Immunotherapy with checkpoint inhibitors has shown promising results, but its role as neoadjuvant therapy is still experimental. PURE-1 study is a phase II study investigating pembrolizumab before cystectomy and showed increased pathological downstaging with patients with PD-L1 CPS $\geq$10% [48]. Interestingly, trials investigating adjuvant immunotherapy have seen the most benefit in luminal infiltrated [49] and basal tumors [50]. Lim et al [51] showed that mutational burden is important also in predicting response to therapy with checkpoint inhibitors, and in particular, ERAP2 is an independent prognostic predictor of survival in patients with luminal subtype bladder cancer receiving anti–PD-L1 therapy, while it has no role for basal tumors. NCT03558087 is currently evaluating the safety and efficacy of neoadjuvant gemcitabine and cisplatin (GC) plus nivolumab NAC and, as a secondary outcome, will determine the association between a prespecified panel of genomic biomarkers and benefit from treatment.

SWOG S1314 RCT is currently examining the analysis of gene expression profiling combined with response to ddMVAC or GC NAC regimens (CO-eXpression ExtrapolatioN—COXEN) [52]. Preliminary data showed that neither ddMVAC nor GC COXEN scores are prognostic for response in individual arms, but the GC score predicts downstaging in combined arms [53].

It should be noted that molecular subtyping has not been tested on variant histology and has not yet been demonstrated to be an intrinsic characteristic rather than a picture of the tumor behavior at that point in time. There is evidence of subtype shifting in different times and intratumor heterogeneity, and there is no constant between genomic alterations and subtyping. Definitive answers on these topics are still needed and might be integrated in the future with analysis of epigenetic modulation.

3.3. Imaging

Imaging is considered a predictive test when performed before the start of NAC, and its potential benefits can arise from its low morbidity and its repeatability even during the midtreatment cycles to evaluate early response. The major limitations arise from poor image resolution in the evaluation of bladder wall invasion. In light of this, bladder

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magnetic resonance imaging (MRI) seems promising although not yet validated [54]. The first evidence regarding the role of MRI to detect response to chemotherapy comes from advanced bladder cancer where improved performance of fast dynamic-contrast–enhanced MRI compared with conventional MRI in distinguishing early responders to MVAC was shown [55,56].

More recently, diffusion-weighted MRI has been utilized with the aim of predicting the response to NAC, because of its capability to provide functional information of tumors, namely, the high cellularity and disorganization of tumor tissue, can be expressed through apparent diffusion coefficient (ADC) values. Lower ADC values before radiotherapy and cisplatin chemotherapy are indeed predictors of chemoradiation sensitivity [57].

In a primary study, Nguyen et al [58] developed a model to characterize the microcirculatory changes within bladder tumors, and found significant changes between responders and nonresponders when comparing MR images obtained at the beginning and at mid-NAC. Subsequently, they evaluated tumor heterogeneity and microcellularity through ADC maps derived from 3 T MRI diffusion-weighted images performed before planned NAC and RC. Fifteen of 20 patients were responders to GC or ddMVAC chemotherapy, and ADC was significantly more heterogeneous ($p < 0.01$) in the nonresponders, meaning that imaging showed higher cellular dishomogeneity; interestingly, initial survival data have shown that the most heterogeneous tumors have also the worst survival outcomes ($p =$ 0.03) [59].

The role of positron emission tomography (PET)/ computed tomography (CT) in MIBC staging is still under debate. Few studies evaluated the accuracy of PET/CT in assessing the response after NAC [60,61], and only one study has analyzed its impact on predicting the effects during the course of NAC where repeated PET/CT identified only four of nine (44%) nonresponders [62].

To our knowledge, no other study has evaluated imaging techniques or parameters to predict the response to NAC.

4. Conclusions

Cisplatin resistance is a complex mechanism that involves different pathways. We provide a summary of current evidence to identify predictors of response to NAC for MIBC. To date, no instrument exists to reliably predict which patients will respond, with increasing evidence suggesting a potential role of DDR genes and molecular classifications that might guide future targeted therapies after further prospective validation. Similarly, MRI aims to characterize tumor patterns, but results are currently limited. In conclusion, there is still insufficient evidence to support a change in the NAC paradigm based on specific response predictors.

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Study concept and design: Motterle, Morlacco, Karnes.
Acquisition of data: Motterle, Morlacco.
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