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Review

The Role of Chemotherapy and Radiotherapy in the Surgical Management of Muscle Invasive Bladder Cancer

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Abstract

The management of muscle invasive bladder cancer represents an unresolved clinical challenge. Invasive urothelial carcinomas are associated with high mortality rates and early metastatic disease. Radical cystectomy is a recognized standard of care, although disease-free survival outcomes remain suboptimal. The limitations of pre-operative clinical staging, as well as the complex natural history of the disease, precludes the introduction of simple management protocols. To what degree chemotherapy and radiotherapy may be useful in the surgical management of invasive bladder cancer remains contentious. This literature review critically examines the benefits, risks and difficulties of each approach, with an emphasis on individually tailored therapy.

Keywords: Chemoradiotherapy, combined modality therapy, urinary bladder neoplasms, cystectomy (Source: MeSH, NLM).

Introduction

Bladder cancer is the fourth most common malignancy in men and the ninth most common in women, with an estimated incidence of 32.5 per 100,000 in the West.[1] The overwhelming majority of bladder cancers in this population arise from urothelial epithelium; approximately 90% are transitional cell carcinomas (TCC). Rarely, squamous cell carcinoma or adenocarcinoma may be seen, in 7% and 2% of cases respectively (although their prevalence is subject to certain geographical parameters). The etiology of bladder cancer remains controversial and various risk factors have been identified, discussed elsewhere.[2,3] Patients are typically elderly (>65 years) and male: few cases are seen below the age of 50 and men are four times more likely to develop the condition.[4]

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The management of bladder cancer remains controversial. Indeed, falling bladder cancer incidence over the last two decades has not been associated with universal improvements in mortality.[5] This literature review will critically appraise the use of chemotherapy and radiotherapy in the surgical management of muscle invasive bladder cancer. Multimodal therapies for non-invasive and metastatic disease fall beyond the scope of this topic. Similarly, specific surgical approaches will only be discussed where appropriate.

Search Strategy and Selection Criteria

A literature review was performed using PubMed, MEDLINE, Science Direct, Scopus and Embase databases using the search terms 'muscle invasive bladder cancer', 'radical cystectomy', 'bladder-sparing surgery' and 'chemotherapy/radiotherapy for bladder cancer'. Randomized studies, reviews and consensus guidelines were included. Additional relevant papers were retrieved from the references. All included articles were in the English language. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[6]

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Stage and Grade

The primary determinant of prognosis is the stage and grade of the lesion, with lesser concern given to size and multicentricity for muscle invasive disease.[7] Clinical staging is based upon a standard TNM classification system.[8] Most tumours (~70%) are non-muscle invasive and, of these, about 70% are confined to the bladder mucosa.

T2 lesions and above are described as 'invasive', having infiltrated the superficial muscle layer at least. Muscle invasion is related to significantly worse outcomes: the natural history (without treatment) in ~85% of cases is death within two years.[9] Additionally, the probability of nodal and metastatic disease is appreciably increased – around 5% of patients present with metastatic deposits. The TNM system for bladder cancer is outlined in ***Table 1***.[8]

The accuracy of available methods for determining the degree of muscle invasion pre-operatively is relatively poor. In fact, the correlation between depth of invasion on cystoscopy and biopsy reports is only in the region of 70%.[10] The limitations of clinical staging are further illustrated in a study of 778 consecutive patients treated with radical cystectomy and pelvic lymphadenectomy: histological up-staging occurred in 42% of patients and down-staging in 22%.[11] However, tissue diagnoses themselves are not always reliable and there remains a significant risk of under-staging following initial resection. Indeed, some studies report that 4-25% of tumours originally classified as non-muscle invasive are actually muscle invasive.[12,13]

The detection of lymph node involvement using imaging techniques is similarly poor. About 20-30% of patients with node negative disease according to computerised tomography (CT) criteria will have pathologically positive specimens at lymphadenectomy.[14] Conversely, a proportion of cases with apparently node positive disease on CT or magnetic resonance imaging (MRI) will be downgraded at the time of surgery. An appreciation of these limitations may influence the relative authority given to surgery over chemotherapy or radiotherapy regimens.

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Table 1. TNM Stage & Grade Classification.[9]

Primary Tumour (T)	
TX	Primary tumour cannot be assessed
To	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
pT2a	Tumour invades superficial muscularis propria (inner half)
pT2b	Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical tissue:
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades extravesical structures
T4a	Tumour invades prostatic stroma, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall
Regional Lymph Nodes (N)	
NX	Lymph nodes cannot be assessed
No	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis
N2	Multiple regional lymph node metastases in the true pelvis
N3	Lymph node metastases to the common iliac lymph nodes
Distant Metastases (M)	
Mo	No distant metastasis
M1	Distant metastasis
Histological Grade (G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media.

Both CT and MRI scans may be used to assess local invasion, although both techniques only reliably detect T3b (extra-vesical) disease or above.[15] Some debate has surrounded the relative authority given to MRI over CT; however, the greater soft tissue contrast afforded by the former now means it is the imaging modality of choice. For example, the accuracy of MRI in primary tumour staging is in the region of 85%, some 20% higher than CT.[16] There may also be a role for fast dynamic contrast-enhanced MRI, especially in differentiating tumour from post-biopsy reactive changes.[17] To avoid this, current consensus suggests that imaging be undertaken before resection in cases where muscle invasion is suspected.[18]

Treatment Options for Muscle Invasive Bladder Cancer

Surgery

Radical cystectomy with lymphadenectomy represents a recognized curative standard of care for muscle invasive disease, or high-risk superficial carcinoma unresponsive to conservative treatment. Bladder-preserving alternatives will not be discussed here, except to highlight that these conventionally employ a multimodal approach in which surgical resection is supported by post-operative chemoradiotherapy.[19]

Epidemiological studies repeatedly demonstrate that radical cystectomy produces the best outcomes, with recurrence free survival at five years most marked in organ-confined invasive cancer.[20,21] Importantly, early cystectomy within a three-month window is associated with improved survival. In a subgroup analysis of patients with ≥T2 carcinoma, one study showed significantly less progression to lymph node positive disease (12% vs. 26%; p<0.013) and enhanced five-year disease-specific survival (80% vs. 56%, p<0.0006) following prompt surgical treatment.[20] Within this 12-week timeframe, however, there appears to be no additional benefit of earlier local therapy.[21]

The factors influencing the type of urinary diversion offered are beyond the scope of this review; however, a recent Cochrane report suggests that no particular technique is convincingly superior.[22] Crucially, the type of reconstructive approach used has no significance with regards to whether chemotherapy or radiotherapy can be offered.[3]

The benefits of an initial surgical approach typically relate to tumour debulking and relief of local symptoms. Perhaps more importantly, surgical resection allows for definitive pathological staging. A larger, more recent trial to that discussed earlier demonstrated misleading clinical staging in 68% of the 3393 patients assessed.[11,23] Removed specimens may be used to establish chemosensitivity profiles, or to stratify the patient into specific risk groups (so as to better inform their decision as to whether to opt for additional therapies). For example, those with pT2 TCC can expect up to 80% recurrence free survival at five years without additional chemotherapy or radiotherapy.[24] Prompt tissue diagnosis is therefore beneficial in this regard.

Chemotherapy: Neoadjuvant chemotherapy

Most bladder cancer patients usually succumb to distant disease. Long-term follow-up of radical cystectomy patients suggests that, despite adequate local control, overall survival for muscle invasive TCC is suboptimal. Only 52-77% of pT2, 40-64% of pT3 and 26-44% of pT4 individuals can expect to survive five years post-surgery.[24] Occult micrometastatic disease during definitive local therapy is thought to underlie these unsatisfactory outcomes; hence, a key benefit of pre-operative chemotherapy is that it may permit early treatment of outlying disease.

Neoadjuvant chemotherapy also allows for an in vivo assessment of tumour response (possibly leading to down-staging and reversion to bladder-sparing surgical options in a subset of patients). In one study of 111 patients with invasive TCC, 54% showed clear transurethral biopsies following MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) therapy.[25] These 60 patients were then allowed to choose between follow-up transurethral surveillance (n=28), partial cystectomy (n=15) or radical cystectomy (n=17). Of the 43 who opted for bladder-sparing options, 74% were alive at ten years and 58% were fully continent. However, 56% developed recurrence and 13 cases required salvage cystectomy. These data demonstrate that the majority of locally advanced carcinomas responsive to chemotherapy are candidates for bladder-sparing intervention at a known risk of recurrence and, of these, most can be treated with salvage cystectomy.

Patient reported outcome measures suggest that conservative, bladder-sparing approaches are preferable to radical cystectomy. A questionnaire-based study of 59 patients demonstrated improved quality-of-life measures in all parameters assessed, the majority of these trends reaching statistical significance.[26] Thus, neoadjuvant treatment followed by bladder-preservation qualifies as a recognized standard of care for a subset of eligible patients. This may be offered to selected patients for their own consideration.

Even if bladder sparing does not become feasible, chemotherapy in the neoadjuvant setting appears to be largely beneficial. For example, the 1999 European Organization for Research and Treatment of Cancer (EORTC) Study suggests that pre-interventional chemotherapy is of value in both radical cystectomy and radical radiotherapy patients.[27] Median survival of patients randomised to the chemotherapy group increased from 37.5 months to 44 months following three cycles of CMV (cisplatin, methotrexate and vinblastine). Despite a higher incidence of pathological complete response in the treatment arm and this trend towards longevity, the failure to achieve a predefined 10% survival improvement criterion meant that these data were originally reported as unsuccessful. Importantly, however, seven-year delayed follow-up revealed a statistically significant hazard ratio (HR) of 0.85 in favour of chemotherapy. The later US Intergroup Trial (SWOG 8710) showed similar improvements in life expectancy: on intention-to-treat analysis of the 317 patients enrolled and randomised, pre-operative MVAC therapy appeared to extend median survival time (46 months vs. 77 months; p=0.06).[28] Advantageous outcomes were strongly associated with clear cystoscopy specimens in both treatment and control groups – of those with pTo at the time of radical cystectomy, 85% were alive at five years. Pathological complete response was in the region of 38% for MVAC candidates – compared to just 15% in the surgery alone control arm – strengthening the causal link between chemotherapy and improved survival.

Two consecutive trials from the Nordic Urothelial Cancer Group further validate pre-operative chemotherapy.[29] Five-year survival in the treatment arm increased from 48% to 56%, corresponding to an absolute risk reduction of 8% and a beneficial HR of 0.80. However, subgroup analysis of patients according to T stage, gender or age revealed no significant differences, thus making it impossible to select which patients are most likely to benefit. However, as these studies tended to recruit younger patients with good renal function and better cancer performance status, their conclusions require rigorous scrutiny.

Overall, the data substantiate a direct link between platinum-based combination neoadjuvant chemotherapy and improved survival measures. Several meta-analyses have since been published, all of which support a modest – but significant – effect. For example, retrospective analysis of 2688 patients collated from 10 studies generated a favourable HR of 0.87 (p=0.016), regardless of the local therapy employed.[30] This translates into a survival advantage of approximately 5% at five years, a figure that has since been repeated in a larger meta-analysis.[31] In this second report, all but 196 of the 3005 patients included received cisplatin, with a 9% improvement in five-year disease free survival. Although the former study includes results from unpublished trials (perhaps undermining the reliability of the dataset used) and both analyses freely aggregate data from various clinical trials with heterogeneous combination cisplatin-based regimens, neoadjuvant chemotherapy appears to be largely beneficial.

But platinum-based chemotherapeutics are not without potential toxicity; indeed, single agent cisplatin has been associated with worse outcomes than surgery alone.[30] However, a systematic review of neoadjuvant MVAC chemotherapy only attributes 1.1% of deaths to this platinum-containing regimen.[32] Equally, evidence from the metastatic setting has shown that GC (gemcitabine and cisplatin) can produce similar response rates at reduced toxicity and, as such, may be of use pre-operatively.[33]

Several small non-randomised studies have lent support to the use of GC. For example, one phase II trial of 22 pre-cystectomy patients found a combined partial and complete radiographic response in 70% of muscle invasive TCCs treated with GC.[34] Of the 15 individuals that went on to have surgery, pathological complete response was evident in 4 (26.7%) of specimens. Median survival was 36 months with no deaths attributed to chemotherapy. Similar results have been reported elsewhere.[35] Although these studies may reasonably reassure that GC may provide a practical alternative to MVAC, neo-GC has yet to be validated in prospective, randomised clinical trials.

Indeed, more recent studies have supported the use of pre-operative "accelerated" MVAC (under hematopoietic growth factor coverage) in muscle invasive disease.[36] This dose dense approach minimises the delay to definitive treatment imposed by more protracted, conventional MVAC or GC therapies and – at present – may be considered the optimal regimen for patients eligible for cisplatin-based chemotherapeutics. Patients deemed unsuitable for typical cisplatin regimens may either receive less intense doses in a modified schedule (with or without nephroprotection), or avoid cisplatin altogether. This is usually achieved by substituting carboplatin for cisplatin, although the efficacy of this alternative remains controversial.[37]

Overall neoadjuvant chemotherapy is associated with a slight survival advantage for muscle invasive bladder cancer. However, it does not allow for the selection of patients most likely to benefit and can only be systematically provided at the known risk of overtreatment. Metastatic disease shows chemoresistance in approximately 40-60% of cases and it is not unreasonable to assume that locally advanced TCC will show similar rates of non-responsiveness. Therefore, neo-chemotherapy may be considered as a standard of care, although clinicians and patients should still be able to elect for definitive local therapy with the option of post-operative chemotherapy.[18]

Adjuvant chemotherapy

As in neo-chemotherapy, the principle of adjuvant drug administration is to eliminate occult metastases beyond the margins of local therapy. It provides two further key theoretical benefits: firstly, definitive treatment is not delayed and, secondly, therapy type can be based upon defined pathological criteria. The ability to risk stratify is key, as those most likely to benefit appear to be those at greatest risk of relapse.[38] Indeed, adjuvant chemotherapy may be especially indicated in certain high-risk patient groups, including those demonstrating residual node and margin positive disease.

One obvious issue with adjuvant approaches is whether patients are sufficiently fit following surgery. Two different studies report post-cystectomy complications in 30-58% of cases, potentially delaying the timely administration of systemic therapy.[39,40]

Several trials have examined the role of adjuvant chemotherapy in muscle invasive disease, producing mixed results. One early trial suggested that post-operative chemotherapeutics were associated with improved time to progression, cancer regression and overall survival parameters within three years; yet the same trends were not seen at five years.[41] This was, however, only a small study of 91 patients, further confounded by non-standard chemotherapy regimens and poor application of treatment (fully a quarter of those randomised to the treatment group never received chemotherapy).[41] Similar issues were encountered in two further trials, both of which were abandoned after inadequate accrual.[42,43] Although these

studies also demonstrated advantageous progression free survival outcomes (HRs of 2.84 and 2.84, respectively), the results are based upon <100 patients. Ethically too, these studies have been criticised – primarily for failing to treat those in the observation-only group undergoing relapse. Long-term follow-up has addressed these concerns and (with a further 117 patients added to the dataset) continue to demonstrate a marked benefit to adjuvant therapy.

A meta-analysis of six such RCTs collated results from 491 patients, revealing an absolute survival improvement of 9% at three years (HR 0.75; p=0.019).[44] Although these data demonstrate the feasibility and safety of adjuvant drug administration, underpowering and inconsistent methodologies prevent the authors from recommending this type of chemotherapy as standard.

Another issue is that many early studies were closed after interim analysis. For example, the EORTC 30994 phase III trial has yet to publish its results (although it too was terminated after poor accrual). Interestingly, this study design permitted the use of MVAC or GC chemotherapy, at the physician's discretion. Recent research has suggested no statistically significant benefit to GC over observation in the adjuvant setting.[45] However, with only 194 patients recruited, even this multicentre trial was underpowered to show the impact of treatment on any endpoint assessed.

There appears to be no compelling role for non-platinum based chemotherapy post-operatively. Gemcitabine alone in patients deemed unsuitable for cisplatin therapy produced a trend towards improved survival and disease-free progression when compared to surveillance alone, but neither outcome measure reached significant thresholds in a recent trial.[46] Similarly, single-agent cisplatin has yet to be validated post-operatively. For example, one small prospective study failed to detect a survival advantage at five years when compared to expectant observation.[47]

Overall, there appears to be low quality evidence to support the utility of adjuvant chemotherapy for locally advanced disease.[48] Therefore, patients with high-risk cancer and/or pathological node involvement who fulfill fitness criteria (and who are willing to accept known toxicity risks without proven survival benefit) might be considered candidates for post-operative treatment. Yet a recent systematic review failed to demonstrate improved survival outcomes – even in selected subgroups with extravesical malignancy.[49]

Identifying those individuals deemed 'high-risk' therefore presents particular challenge. One novel idea revolves around selection by p53 status (with several retrospective studies suggesting that p53 changes may be prognostic for TCC recurrence and adjuvant MVAC efficacy). Immunohistochemistry for p53 expression segregated one study population into two groups, either managed conservatively or with three cycles of chemotherapy.[50] Although the authors note a high-rate of non-compliance with the original study design, p53 status appeared to have no meaningful effect on endpoint outcomes.

Radiotherapy

The potential advantages of radical radiotherapy as definitive treatment include bladder preservation, avoidance of surgery and intact sexual function. Observational studies suggest that this modality provides five-year survival rates in the region of 28-50%,with successful salvage cystectomy in ~20% of failed cases.[51,52] Although direct comparison with radical cystectomy is challenging, large surgical and radiotherapy series report similar long-term survival outcomes.[53]

The marginal superiority of scheduled surgery is supported by two meta-analyses. In the first, three RCTs demonstrate a five-year survival benefit to pre-operative radiotherapy and planned cystectomy over radical radiotherapy with secondary salvage cystectomy.[54] A second Cochrane review corroborates these data, although the calculated odds ratio of 0.71 was sufficient only to suggest a trend rather than significance.[55] However, the advancing age of these particular studies questions whether their findings can be applied to more modern techniques.

No RCTs directly compare radiotherapy to chemotherapy as single modalities in bladder cancer. However, one early phase II study demonstrated a modest advantage to chemoradiotherapy over radiotherapy alone, both in terms of ten-year survival and bladder preservation rates.[56] Should patients prefer radical radiotherapy with the intention of bladder sparing, it is important that they appreciate an increased risk of complications during salvage cystectomy. For example, one small study of 23 patients reported higher complication rates in those with a history of external beam irradiation versus a control matched planned-cystectomy group (48% vs. 26%; p<0.045).[57] Thus, cystectomy after failed radiotherapy comes with a recognized morbidity risk.

As in chemotherapeutic approaches, it would be of value to be able to identify those patients most likely to benefit in advance. One retrospective analysis of 342 patients with a median 7.9-year follow-up highlighted tumour multiplicity (p<0.001), ureteric obstruction (p=0.001) and higher T stage (p=0.004) as independent prognostic factors in relapse rates.[58] Those patients with these features might be better discouraged from radical radiotherapy, whereas younger patients with high-grade exophytic tumours appear most likely to respond.

Further research might aim to advance our understanding of these predictive markers, or investigate optimal dose, fractionation and scheduling considerations in treating locally invasive disease. Although a recent phase III trial (BC2001) assessing the viability of reduced high-dose volume radiation therapy failed to formally demonstrate noninferiority of locoregional control and a reduced side effect profile, additional studies in this area are required. For example, the theory that 'accelerated radiotherapy' minimises repopulation by surviving clonogens has yet to be rigorously tested.[59]

If radiotherapy is to be delivered with curative intent, the European Society for Medical Oncology (ESMO) advises that external beam radiotherapy should be delivered with 3D conformal or intensity-modulated techniques, ideally under image guidance.[18] Typically, this would be provided in conjunction with a multimodal bladder-preserving approach.

Synchronous Chemoradiotherapy: Bladder Preservation

Radiotherapy alone is a recognized bladder-sparing alternative to cystectomy in patients with muscle-invasive disease, yet it remains associated with a relatively high rate of incomplete response or local recurrence. Synchronous chemoradiotherapy may therefore have advantages over radiotherapy alone and may be especially useful in the treatment of those patients unfit for major surgery. This is supported by evidence from other primary cancer sites, including cervical and anal malignancies.[60,61]

A recent multicentre phase III trial demonstrated that that concomitant chemotherapy (with fluorouracil and mitomycin C) and radiotherapy significantly improved locoregional control of muscle-invasive disease when compared with radiotherapy alone.[62] The

addition of chemotherapy to standard-dose radiotherapy was associated with a relative reduction of 33% in the risk of locoregional recurrence and almost 50% in invasive recurrence. Improved locoregional control was achieved with only modest increases in toxic effects that did not achieve statistical significance with respect to grade 3 or 4 outcomes. Long-term follow up revealed a clear advantage for those patients randomised to the chemoradiotherapy group: at 5 years, overall survival rates were 48% in the experimental arm versus 35% for those receiving radiotherapy alone. This was achieved without increased rates of salvage cystectomy. Further research might seek to establish whether synchronous chemoradiotherapy is preferable to radical cystectomy as definitive treatment.

This study also contributes two further important observations. Firstly, that the benefits of synchronous chemoradiotherapy were independent of a history of neoadjuvant chemotherapy – suggesting that neoadjuvant and concomitant chemotherapy confer separate benefits on distant and local control, respectively. Secondly, fluorouracil and mitomycin C in combination are effective radiosensitising agents and may be considered for patients unfit for cisplatin-based therapies. This adds to previously proposed alternatives to radiosensitisation based on tumour hypoxia, typically induced by the use of nicotinamide and carbogen.[63] Together, these trials suggest that it may be time to re-evaluate the preference for surgery over bladder-sparing options, particularly in those patients at high-risk for surgical complications.

Trimodal Therapy: Bladder Preservation

Trimodality treatment – i.e. combining chemoradiotherapy with bladder-sparing surgical options – may also represent a viable alternative to radical cystectomy in muscle-invasive bladder cancer. For example, two prospective studies in which chemoradiotherapy was augmented by transurethral resection demonstrated that this approach could be safely applied in selected patients.[64,65] Accurately identifying those individuals most likely to benefit may well be difficult, although tumour grade and status after the initial resection appear to be important prognostic factors.[65]

Bladder-preserving multimodal approaches demand a high level of multidisciplinary cooperation and patient compliance. Meticulous long-term surveillance is required to detect intravesical tumour recurrences and this should be considered when offering bladder-sparing options. This decision may be further informed by several clinical criteria, including: early tumour stage, a visibly complete or maximally debulking TURBT, absence of associated carcinoma in situ (CIS) and adequate bladder capacity and function.[66] If persistent or recurrent disease is identified during response evaluation or follow-up, prompt salvage cystectomy is required.

Discussion

Even with accurate staging information, the appropriateness of various different management options remains contentious. For example, the National Comprehensive Cancer Network (NCCN) and NHS guidelines detail at least four separate care plans for the treatment of primary cT2 disease, summarized in ***Table 2***.[67] This highlights the need for individually tailored therapy, with consideration given to factors such as age and comorbidity, as well as patient preference. In the absence of convincing evidence to support one approach over another, it is perhaps this last component that primarily directs therapeutic strategy.

NCCN and ESMO guidelines both advocate radical cystectomy with extended lymphadenectomy as the standard treatment for muscle invasive bladder cancer without nodal involvement.[18,68] Those patients with a good performance status and intact organ function should be strongly considered for neoadjuvant cisplatin-based combination chemotherapy, whereas those unfit for surgery should be considered for radiotherapy either with or without chemotherapy. A small minority of patients (<5%) with a solitary T2 lesion in a suitable location without concurrent CIS may be eligible for partial cystectomy, usually in conjunction with neoadjuvant chemotherapy. Partial cystectomy is not an option for patients with T3 disease or above.

In both post-cystectomy patients and those pursuing bladder-sparing options, follow-up is an essential component of long-term management, although protocols vary worldwide.[18,68] As a minimum, urine cytology and imaging of the chest, abdomen and pelvis should be performed every 3 to 6 months for 2 years and then as clinically indicated. Routine bloods include creatinine, electrolytes and liver function tests. Urethral wash cytology is recommended if urethrectomy has not been carried out and/or there is a history of CIS.

Follow-up of patients opting for partial cystectomy or other bladder-sparing approaches is the same as for radical cystectomy, except that these individuals require additional 3-monthly surveillance by cystoscopy (usually with selected mapping biopsies) for the first 2 years at least. Continued monitoring for recurrence is especially important, as most are superficial and therefore readily amenable to endoscopic treatment.

Conclusion

The management of muscle invasive bladder cancer remains controversial. The advent of better profiling methods using high throughput technologies might aid in staging, prognosis and selection of optimal treatment approaches;[69-71] until then, management pathways are guided by an often inconsistent and unclear literature base. However, the value of reliable research is as much in guiding the patient as the clinician. Protocols for invasive urothelial cancers incur known morbidity and mortality risks and, ultimately, informed patients must be involved in the decision-making process.

Table 2. Summary of Primary Care Protocols for cT2 Disease.

Treatment Option	Notes
Radical cystectomy with urinary diversion	Strongly consider neoadjuvant cisplatin-based combination chemotherapy
Segmental/partial cystectomy	Consider neoadjuvant cisplatin-based combination chemotherapy
Selective bladder sparing following maximal TURBT	Consider concurrent radiotherapy and chemother-apy ± salvage cystectomy
TURBT alone or radiotherapy alone or chemotherapy alone	Extensive comorbidities/poor performance status

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