The increasing indications of FDG-PET/CT in the staging and management of Invasive Bladder Cancer

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Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Keywords: bladder cancer; FDG-PET/CT; neo-adjuvant chemotherapy; staging; lymph node mapping; pelvic lymph node dissection

Word count of the abstract: 159 words

Word count of the manuscript: 3589 words

Abstract

Context:

The management of locally advanced Muscle Invasive Bladder Cancer (MIBC) often necessitates neo-adjuvant chemotherapy (NAC) to eliminate any micro-metastatic disease prior to definitive radical cystectomy (RC) and pelvic lymph node dissection (PLND). The use of new imaging techniques, such as FDG-PET/CT, enables more accurate initial staging of bladder cancer. In addition, it appears to be better at assessing cancer response to NAC, compared to the more traditional CT and MRI imaging, which is crucial for definitive peri-operative surgical planning.

Objective: Review the evolving indications of functional F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in MIBC.

Conclusion: FDG-PET/CT is being increasingly utilised in local nodal staging and detection of metastatic disease in MIBC. Furthermore, it appears more accurate than conventional imaging modalities (CT/MRI) in assessing tumour response to NAC. This enables the earlier detection of tumour response and/or residual disease, impacting factors such as the duration of chemotherapy, with its associated adverse effects, and the timing of surgical intervention.

Introduction

Bladder cancer is the second most common urogenital malignancy, preceded by prostate cancer. It is the sixth most common cancer in men and the seventeenth most common cancer in women. Cigarette smoking is the most significant modifiable risk factor whereas age and family history comprise the most significant non-modifiable counterparts. About 90% of bladder cancer in developed countries have a urothelial origin (transitional cell carcinoma), while squamous cell carcinoma is more prevalent in developing nations.

Management strategies and prognosis of bladder cancer depends on the extent of the locoregional disease and categorisation into non-muscle invasive disease (≤T1 stage) and muscle invasive disease (≥T2 stage), which account for 75% and 25% of cases respectively. [1] Annually, 275,000 people are diagnosed with this disease and 108,000 die from it. Non-muscle invasive disease is managed surgically with transurethral resection of the tumour with or without photodynamic chemotherapeutic adjuvants.[2]

The standard of care for muscle-invasive disease which is amenable to surgical treatment (cT2-T4aN0M0) is radical cystectomy (RC). It is recommended in patients with a longer life expectancy without concomitant disease and a higher performance score (PS). Among neoadjuvant chemotherapy (NAC) options, platinum-based options such as cisplatin combinations are preferred, if eligible. If ineligible, immunotherapy can be offered, on a trial setting. Radiotherapy (RT) is not recommended. [3,4]

If refractory to NAC, patients with organ-confined disease (cT2-T4aN0M0), are more likely to benefit from direct radical cystectomy rather than NAC. Assessing NAC response is

therefore essential to the peri-operative management of these patients. For this reason, non-invasive imaging techniques such as ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) have been developed. Initially, its use was limited due to the high urinary excretion activity of the ureters and bladder. However, recent studies suggest that this technique can aid the detection of both lymph node metastases as well as distant metastases. [5]

Finally, in patients with lymph node metastases (cT2-T4aN1-2M0), chemotherapy-induced downstaging of the primary tumour can be offered, which has been shown to confer a strong survival benefit. [6] However, persistence of lymph node metastases, post-induction chemotherapy, is associated with poor prognosis, with radical cystectomy often being performed with palliative rather than curative intent. [7]

Therefore, the main objectives of our review paper is to assess the usefulness of ^{18}F-FDG PET/CT in the pre-clinical and post-treatment staging of bladder cancer, with a focus on its ability to evaluate response to NAC. We will also review established techniques for accurate sentinel lymph node mapping and their use in pelvic lymph node dissection.

Cystectomy

According to the European Association of Urology (EAU) and American Urological Association (AUA) guidelines, in developed countries, radical cystectomy is the standard treatment of care for localised muscle-invasive bladder cancer (MIBC; T2-T4a, cN0-Nx, M0) and should be performed within 3 months of initial resection. [4,8–10] Other indications include recurrent high-risk, non-muscle invasive bladder cancer (NMIBC), BCG-relapsing and BCG-unresponsive NMIBC, in addition to extensive papillary disease that cannot be managed with trans-urethral resection and intravesical therapy alone. [11] Salvage cystectomy is preserved for non-responders to conservative therapy, non-urothelial carcinomas, recurrence after bladder-sparing treatment, or for palliative purposes.

The typical procedure performed is a cystoprostatectomy in men and a cystectomy, with or without a hysterectomy, in women. This is followed by the formation of a continent or incontinent urinary diversion, depending on patient preference and contra-indications. Where possible, sexual function preserving procedures should be discussed with patients who meet the requirements of organ-confined disease lacking any bladder neck, urethra or prostate involvement. [1] Options include prostate, capsule, seminal and nerve-sparing techniques in men, although, there is a paucity of data regarding pelvic organ preservation in females.

An important component of RC, that facilitates pathological staging and may have a therapeutic role, is a simultaneous standard or extensive bilateral regional pelvic lymph node dissection (PLND). However, the extent of dissection, number of nodes required, and the anatomical boundaries remain controversial. Currently, there is limited evidence that extended PLND significantly improves recurrence-free or overall survival, with the LEA trial

failing to show a statistically significant improvement in recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS). [12] A larger prospective randomized-controlled trial undertaken by the Southwest Oncology Group comparing standard with extended pelvic lymphadenopathy should provide further insight once completed in August 2022. [13,14]

This brings up an interesting statistical phenomenon known as the Will Rogers which introduces significant bias in the analysis of even the most contemporary studies assessing the beneficial role of extended PLND in bladder cancer. This phenomenon refers to the reclassification of patients to different disease stages because of newer diagnostic techniques (limited vs extended PLND) which ultimately leads to stage migration and misinterpretation of the resulting survival statistics as patients are re-classified from less to more severe metastatic disease. As a result, this can yield a significant improvement in stage-specific prognosis, even though there is no change in the outcome of the individual patients. [15]

Traditionally, radical cystectomy has been performed via an open approach, but, more recently minimally invasive techniques have gained popularity, including both laparoscopic and robotic-assisted approaches. Recent evidence suggests that these minimally invasive techniques are a feasible and safe alternative to open radical cystectomy (ORC), when performed by high volume experienced surgeons in selected patients. [13] In particular, the RAZOR randomised trial confirmed that the robotic approach is non-inferior to the open approach, in terms of 2-year progression-free survival. [16] This was further confirmed by the Cochrane review which identified similar outcomes for robotic cystectomies, compared to the open approach, in terms of time to recurrence, major complication rates, quality of life and positive margin rates. [17]

Chemotherapy

MIBC (T2-4a, N0, M0) treated with RC only confers a 50% 5-year survival. Since the 1980s, platinum-based NAC has been used to enhance outcomes (8% improvement at 5 years). [18,19] Two common regimens currently used for urothelial carcinomas are methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) and gemcitabine, cisplatin (GC).

MVAC was the first recognised option for patients with locally advanced or metastatic urothelial cancer, administered with a 4-week cycle. This was later modified to a dose-dense regimen, administered in 2-week cycles. This led to fewer dose delays and a more favourable toxicity profile associated with a significant improvement in overall survival. [20] GC is a newer regimen which is currently being considered as some studies have shown that it has a more favourable toxicity profile. However, it is unclear whether it enhances complete pathologic response and progression free survival. [18,21,22]

Pre-clinical bladder cancer staging and the role of Positron Emission Tomography (PET)

The prognosis and treatment strategies offered to patients with bladder cancer is dependent on the tumour stage and grade. [23] Carcinomas can be defined as low or high grade based on their histology whilst staging is based on the Tumour, Node, Metastasis (TNM) Classification. Knowledge of vascular or lymphatic invasion also aids in the decision making as it is an independent prognostic indicator. [24]

At diagnosis, 10-15% of patients with urothelial carcinomas were found to have distant metastatic disease at the point of diagnosis and 50% of those with true localised disease eventually developed metastatic lesions within two years, despite aggressive therapy. [25] The most common techniques traditionally used to aid staging are computerised tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis. They are routinely used prior to transurethral resection of the bladder tumour to establish the extent of local invasion as well as progression to lymph nodes, upper urinary tract, or distant organs. [26] However, despite their effectiveness in detecting primary bladder disease, both have a low sensitivity for nodal staging, thereby rendering them impractical to use in this setting. [25,27,28]

A possible solution to the above is ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET)/CT which confers whole-body imaging. This modality exploits the increased utilisation of glucose by malignant cells and by extent, their high glucose uptake and enables clinicians to identify regional and distant metastases as well as cancer recurrences before they become evident by conventional imaging modalities. Despite these benefits, widespread adoption of this radiotracer-guided imaging has remained slow. Initial concerns around the high urinary excretion of ^{18}F-FDG in the bladder and ureters (which can mask bladder lesions and regional metastatic lymph nodes), and substantial overlap of the standardized uptake values (SUVs) from the active inflammatory process and the malignant lesion has limited its use. This is exemplified by small sample studies which have suggested that FDG/PET CT does not confer the appropriate diagnostic accuracy required for the identification of regional lymph node metastasis. [29,30]

To overcome these limitations, simple, non-invasive protocols have been proposed. For example, oral rehydration with forced diuresis enhances the elimination of the ^{18}F-FDG

radiotracer without interfering with its uptake by the vesical tumour. [31,32] Moreover, to improve the diagnostic accuracy of the PET/CT itself, radiological protocols such as the combination of the axial-based lymph node (LN) size and SUV_{max} criteria were incorporated. [33] Over time there has been an increasing amount of evidence to suggest that ^{18}F-FDG PET/CT provides a high sensitivity and specificity in the pre-operative detection of bladder cancer as well as lymph node metastases, pelvic lesions and distant metastases. [33–35]

Further large, randomised controlled trials are required to verify these findings, but, for now ^{18}F-FDG PET/CT has been shown to influence the management of patients and is an important prognostic indicator for progression-free survival (PFS) and overall survival (OS). [36,37] Its significance is further exemplified by a recent consensus statement by the European Association of Urology (EAU) and the European Society for Medical Oncology (ESMO) which stated that ^{18}F-FDG PET/CT should be included in oligometastatic disease staging to minimise the risk of overtreatment, when radical treatment options are being considered. [25] Thus, molecular imaging is essential to accurately stage and evaluate response to treatment, avoid unnecessary aggressive interventions and maximise quality of life.

Restaging bladder cancer and the role of Positron Emission Tomography (PET)

Patients with newly diagnosed MIBC (T2–T4aNXM0) are routinely offered NAC as it has been shown to improve survival through tumour down-staging as well as increasing the likelihood of a pathological complete response (pCR; i.e. pT0). [38] Even if LN metastases are present at initial staging, pCR following NAC is associated with a 5-year cancer specific survival of up to 64%. [6] However, if LN metastases persist despite NAC, patients have a bleak prognosis and cystectomy is not always the most appropriate management option. [9] As

a result, chemotherapy-induced downstaging might be a potential surrogate marker for chemosensitivity and overall survival. [39]

Despite its benefits, NAC is associated with significant risks, like every treatment, which include chemotoxicity and more importantly a delay in the radical treatment of chemo-resistant tumours, chiefly through direct radical cystectomy. Bhindi et al found that patients with residual tumour post-NAC and cystectomy have worse overall survival (OS) and cancer-specific survival (CSS) compared to matched controls of similar disease stage with nil NAC. [40] To date, there is no consensus recommendation regarding restaging imaging during NAC to identify chemo sensitive tumours. In fact, the EAU guidelines go one step further by stating that there is no evidence for the use of CT in the assessment of NAC-responsiveness in patients with MIBC. [4,27,28] Identification of techniques with a high sensitivity to NAC-response as well as recurrence detection is therefore warranted to enhance patient survival, limit chemotherapy-related side-effects and improve quality of life. [41]

Currently, traditional techniques used for follow-up and restaging include a combination of cystoscopy, urine cytology, routine blood tests and imaging such as CT or MRI scans. Whilst the CT evaluates the intravesical recurrence, the MRI assesses the presence of nodal or distant metastases. ^{18}F-FDG-PET/CT is a relatively new technique that reliably monitors response to chemotherapy in various cancer types and is more accurate than conventional imaging (Table 1). It allows early visualisation of metabolism alternations, which occur before morphological changes become visible. [42]

Diagnosis	Allows better assessment of a patient's response to NAC
	Used in detection of both Lymph node metastases and distant

	F-FDG is used for whole-body imaging, and utilises the increased use of glucose by malignant cells – which clinicians can use to identify local/distant metastases before they are signalled by conventional imagining modalities
	Improved diagnostic accuracy of PET/CT, and F-FDG PET/CT by combinations of axial based LN size and SUV_{max} criteria allowed high sensitivity as well as specificity in pre-operative detection of bladder cancers, lymph node metastases, pelvic lesions, and distant metastases
	Imaging here allows early visualisation of metabolism alternations
	It has an 83% sensitivity with a 94% specificity for the detection of chemo-sensitive tumours
Follow up	F-FDG-PET/CT proven to reliably monitor response to chemotherapy in various cancers
	High efficacy in bladder cancer, with a 92% sensitivity of F-FDG-PET/CT in detecting residual invasive bladder cancer, and a 95.2% accuracy in detecting post-treatment recurrence outside the urinary tract, especially for bone lesions
	FDG-PET/CT has a sensitivity and specificity of 78.5% and 95.6% respectively in identifying complete pathologic response
Treatment	F-FDG-PET/CT shown to influence patient management and is a prognostic indicator of PFS and OS
	F-FDG-PET/CT should be included in oligometastatic disease staging to minimise the risk of overtreatment, when radical treatment options are being considered
	Currently recommended by the American College of Radiology for patients with MBIC (from skull-base to mid-thighs)

Table 1. The evolving indications of FDG-PET/CT in muscle-invasive bladder cancer based on the current recommendations of the European Association of Urology, European Society for Medical Oncology and American College of Radiology Appropriateness Criteria. [14, 26, 49]

A recent meta-analysis by Xue et al. identifies FDG-PET/CT as an effective method to detect both residual and recurrent disease. [43] Higashiyama et. al confirmed a 92% sensitivity of ^{18}F-FDG-PET/CT in detecting residual invasive bladder cancer. [44] When compared to the conventional re-staging technique i.e. contrast-enhanced CT, FDG-PET/CT maintained its superior accuracy in detecting post-treatment recurrence outside the urinary tract, primarily bone lesions, with an accuracy of 95.2%. [45]

When used to assess response to induction chemotherapy, FDG-PET/CT was found to have a sensitivity and specificity of 78.5% and 95.6% respectively in identifying complete pathologic response and 83% and 94% respectively for the detection of chemo-sensitive tumours. [46] Abrahamsson et al. further investigated the usefulness of this technique in patients with LN-positive MIBC by identifying an association between pCR and increased PFS and CSS. [47]

Furthermore, the updated 2021 American College of Radiology Appropriateness Criteria recommend the use of FDG-PET/CT from the skull-base to mid-thigh in patients with MIBC as it has been shown to have prognostic significance. [48] Further large-cohort randomised trials would ideally be required to confirm its usefulness and routine usage as small-cohort studies provide conflicting evidence regarding its accuracy in detecting LN metastasis post-NAC. [49]

Pelvic Lymph Node Dissection

Pelvic lymph node dissection (PLND) enables appropriate staging of bladder cancer along with prognostic information. LN metastases are identified in 20-25% of patients at the time of RC, hence conferring poor oncologic outcomes and triggering administration of adjuvant cisplatin-based chemotherapy, if NAC was not given. [1,8,9] Appropriate clearance of these metastatic nodes is therefore essential to improve CSS and OS. Yet the optimal extend of PLND has not been established to date. [15]

A contributing factor is that many studies use a template system consisting of limited, standard, extended and super-extended resection. Whilst these phrases are commonly used, they do not consistently refer to the same anatomical boundaries. Limited PLND classically refers to a dissection restricted to the obturator fossa bilaterally. Standard PNLD includes removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border. It also includes removal of the internal iliac, presacral, obturator fossa and external iliac nodes. Extended PLND includes all areas previously mentioned and all LNs in the region of the aortic bifurcation as well as the presacral and common iliac vessels, medial to the crossing ureters. The genitofemoral nerves form the lateral borders whilst the circumflex iliac vein, lacunar ligament and LN of Cloquet form the caudal extension. Super-extended PLND extends the dissected area caudally to the level of the inferior mesenteric artery. [50,51]

Li et al.'s meta-analysis identified a statistically significant survival advantage for bladder cancer patients following RC in patients with a greater number of dissected lymph nodes. [52] The number of LNs dissected could therefore be an independent prognostic indicator in

bladder cancer and would validate the theory of enhanced outcomes with extended PLND. This is supported by Alveus et. al's multicentre analysis which identified a higher average number of tumour-draining sentinel lymph nodes in patients treated with NAC who belonged to the Complete Response rather than the Progressive Disease cohort, thereby implying that the number of positive LNs is directly proportional to the strength of the immune system. [53] Conversely, whilst submission of separate nodal packets instead of *en-block* has shown a significant increase in total LN yield, this was not associated with an increased number of positive LNs, making LN density an inaccurate prognostic indicator. [54]

Approximately 41% of metastatic lymph nodes are outside the confines of the standard PLND template, implying that an extended or super-extended PLND would yield superior oncological outcomes. [51] Wang et al. supported this hypothesis with a favourable long-term prognosis identified in patients undergoing extended PLND. [55] However, when the super-extended approach was compared to the extended PLND template, no oncological benefit was noted, which may be because metastatic spread beyond the anatomical pelvis increases the risk of visceral and nodal deposits beyond the super-extended template. [51]

The LEA trial, a recent prospective phase III randomised controlled trial (RCT) assessing extended versus limited LND, failed to identify a significant improvement of recurrence-free survival (RFS; aimed to show an absolute improvement of 15% for the 5-year RFS), CSS and OS in patients with extended LND. [12] The disparity of "extended" and "limited" PLND definitions between studies, combined with the multimodal approaches to treatment with neo-adjuvant and adjuvant chemotherapy and specifics on how studies were powered complicate these results. Results from a prospective RCT performed by the Southwest Oncology Group

(SWOG), which is fully accrued but not yet reported, may shed further light as to the therapeutic role of extended PLND. [14]

Lymph Node Mapping

Bladder lymphatic flow and cancer spread to LNs is difficult to predict and innovative techniques are required to enhance the existing techniques and improve surgical outcomes. Sentinel LN (SLN) mapping can aid the resection of selected, invaded LNs, thus easing histopathological examination, instead of performing a "blind" template LN resection in the form of limited, standard, extended or super-extended PLND. SLN biopsy (SLNB) has been successfully incorporated in clinical practise for the treatment of breast and skin cancer and has contributed to a reduction in the extent of lymphadenectomy, improved oncologic outcomes and limited surgical complications.

Unfortunately, the lymphatic drainage pattern of the pelvis is complicated, and the bladder sentinel drainage is highly variable, with nodes often being identified unilaterally or bilaterally. This bilateral distribution of SLNs can happen independent of the tumour position and is named the Crossover phenomenon. It may be due to simultaneous SLNs arising from different tumour parts and anatomically different lymphatic routes in patients. Hence accurate lymph node mapping is essential.

Currently, the most common dyes used for SLN mapping are technetium-labelled radiocolloids (Tc-RadCol), blue dye and indocyanine green (ICG). The standard technique to detect LNs using these methods is to use a gamma probe for Tc-RadCol, a near-infrared fluorescent (NIRF) camera for ICG and direct visualisation for the blue dye. [58]

Zarifmahmoudi et al. identified a high detection rate and sensitivity for SLNB in MIBC and showed that low pT stage bladder cancers with clinically negative LNs, are the most appropriate group for SLN mapping. [56] A comparative study assessing the usefulness of Tc-RadCol and ICG in the evaluation of LNs in bladder cancer identified that both techniques are useful, with the ICG fluorescent technique allowing a safe, live view of the results, at no additional cost. [57]

How et al. further confirmed these findings through a comparative study for all 3 agents – Tc-RadCol, ICG and blue dye – in endometrial cancer. ICG was found to be superior to blue dye and comparable to Tc-RadCol. It also showed that a combination of ICG and Tc-RadCol enables a high detection rate of SLN, with the blue dye not being essential for SLN detection. [58] A hybrid tracer utilising the radioactivity of technetium and the fluorescence of ICG may be ideal moving forward.

There is evidence to suggest that combining FDG-PET/CT with traditional SLN techniques can be a promising diagnostic approach, capable of enhancing the pre-operative LN assessment by identifying safe candidates for SLNB. A recent national multicentre study performed by Jakobsen et al. in Denmark has shown a reduction in the false-negative rate in penile cancer patients from 11.8% to 5.6% when SLNB was used in conjunction with FDG-PET/CT. However, there is a lack of large-cohort studies assessing the safety, viability and effectiveness of this technique in bladder cancer LN mapping. [59,60]

Conclusion

The management of muscle invasive bladder cancer requires a co-ordinated multi-disciplinary approach. The use of FDG-PET/CT imaging allows for improved nodal staging and detection of metastatic disease, thus enabling earlier identification of patient response to NAC when compared to the traditional imaging modalities (CT, MRI). The risks associated with potential overtreatment and chemotherapeutic side effects may be mitigated and definitive radical treatment can be undertaken in a timely fashion. The evolving indications of FDG-PET/CT, both initially at diagnosis as well as during and post treatment with NAC, is exciting, although further studies, including randomised controlled trials, are required to reliably assess its impact on both overall and disease-free survival.

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