The National Institute for Health and Care Excellence (NICE) guidance on bladder cancer. A step in the right direction?

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Bladder cancer is the 7th commonest cancer in the UK accounting for 5,369 deaths in 2014 [1]. Over the last decade, despite improvements in other cancers, bladder cancer survival has remained static [2, 3]. Treatment of incurable metastatic disease remains challenging, with cisplatin-based combination chemotherapy providing only 14 months median survival [4]. Bladder cancer and its treatment can have a significant detrimental impact on patient quality of life and mental wellbeing [5-7], with reported patient experience and satisfaction scores worse than for other cancers [8, 9]. This may be compounded by variations in treatment utilisation throughout the UK [10].

To try to address this variation and provide clarity on acceptable standards in routine practice within the National Health Service (NHS) in England, the National Institute for Health and Care Excellence (NICE) published guidance in February 2015 (Bladder cancer: diagnosis and management, https://www.nice.org.uk/guidance/ng2) [2]. Within the guidance the wording of the final recommendations denotes the certainty with which they are made. The word 'offer' anticipates such interventions will be routinely undertaken, while 'consider' suggests less certain benefit, when 'the healthcare professional should spend more time considering and discussing the options with the patient'.

The British Uro-Oncology Group (BUG), formed in 2004, is the only dedicated professional association for British uro-oncologists providing a forum for discussion on research and policy. The BUG 12th Annual Meeting undertook an interactive multidisciplinary panel discussion to determine adherence to key NICE guidance recommendations, based on pre-specified questions to an audience of UK uro-oncologists, urologists and nurse specialists summarised here.

Question 1: 'Do you have a bladder cancer specific clinical nurse specialist (CNS)?'

Whilst the guideline recommends offering the support of an experienced CNS who has undergone training in bladder cancer care, only 21/83 (25%) of participants indicated that they were able to offer this. From the panel discussion it was noted that most hospitals have general urology CNS provision but that these roles were often conceived to cover different tumour types, with difficulty in providing dedicated bladder cancer support. National Cancer Patient Experience Surveys demonstrate that people with bladder cancer had a poorer experience than those with other urological cancers, and were least likely to have been provided with a cancer specific CNS [8, 11]. As provision of a cancer specific CNS is associated with higher patient satisfaction scores [11], the panel felt this was an important recommendation and should be a key priority.

Question 2: 'What proportion of patients at your centre with localised muscle invasive bladder cancer (MIBC) have a discussion within both urology and oncology about treatment options?'

The NICE guideline recommends offering a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with MIBC cancer for whom radical therapy is suitable, and

that this should be based on a discussion between the patient and both urologist and clinical oncologist. The guideline enshrines the concept that to become 'informed' a person requires a discussion about their treatment options delivered by the specialists that undertake them. Whilst it was recognised that a discussion with both urology and oncology may not be appropriate for certain patients, only 47/77 (61%) of participants indicated that >75% of their patients had a discussion with both specialties. The panel felt that both the survival benefit from neoadjuvant chemotherapy [12, 13], and evidence for bladder preservation by radical chemo-radiotherapy as an alternative to cystectomy in appropriately selected patients [14], made these discussions important. Although evidence is limited, the panel view was that both resource availability and entrenched positions (regarding value of surgery or radiotherapy) were likely contributory factors.

Question 3: 'Do you utilise FDG PET scans within routine staging for bladder cancer?'

Accurate staging is required to facilitate discussion of disease risk and the likelihood of cure from potential interventions. In one study FDG PET with CT upstaged 19.8% of patients, with 8.5% having treatment changed from curative to palliative intent [15]. The guidance recommends considering its use for people with MIBC or high-risk non-muscle-invasive bladder cancer (NMIBC) before radical treatment if there are indeterminate findings on CT or MRI, or a high risk of metastatic disease (for example, T3b disease). Only 13/78 (17%) of participants indicated they used FDG PET scans for bladder cancer staging to guide management of locally advanced disease. The panel were not fully convinced of the utility of FDG PET, and felt further studies were warranted. Newer emerging PET tracers may prove more beneficial for patients in the future.

Question 4: 'Do you offer neoadjuvant chemotherapy (NAC) in appropriate patients?'

The level 1 evidence in support of combination cisplatin based NAC demonstrates an absolute overall survival benefit of 5%. Despite this, concerns persist that NAC is underutilised [16]. In an audit of UK practice between 2004 and 2012 over a third with a suitable indication underwent NAC [17]. The NICE guidance recommends offering NAC to suitable newly diagnosed patients [18-20]. Encouragingly, 66/81 (81%) of participants indicated that they always gave NAC to 'appropriate' people, with all other responding participants indicating they 'sometimes' used it. Taking into account patient suitability, the panel were encouraged by the response to this question, suggesting increasing NAC use in the UK, although coverage may as yet be incomplete.

Question 5: 'Do you offer adjuvant chemotherapy (AC) in appropriate patients?' and 'What would your criteria be for offering adjuvant chemotherapy?'

The evidence is stronger to support NAC (Level 1) compared to AC. For an adjuvant approach, a meta-analysis of 945 patients from nine controlled trials found that AC resulted in improved survival [21]. However on closer analysis, none of the analysed trials recruited to completion and some were unpublished. To date no single, methodologically adequate, phase III trial has been completed in this setting. The NICE guideline reflects this finding in its wording of 'consider' adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive bladder cancer who were not eligible for neoadjuvant chemotherapy, thus positioning NAC as the standard approach but allows for AC, for example, after upstaging to MIBC at cystectomy.

21/78 (27%) of participants always gave AC; 51% sometimes gave it. If, following radical cystectomy, the pathology was upstaged from NMIBC to MIBC, 22/73 (30%) of participants

indicated they would offer AC. While 60% would offer it to high risk patients that did not receive NAC, 10% would offer it to patients with persistent disease despite NAC. The panel felt there was little evidence to support the latter option.

Question 7: 'Do you routinely offer radiation with a radiosensitiser or radiotherapy alone, assuming the patient is fit for this?' and 'What is your choice of chemo-radiation regimen?'

Radiotherapy with a concurrent radiosensitiser improves outcomes over radiotherapy alone and the NICE guideline endorses this. Encouragingly, 61/74 (82%) of participants indicated that they routinely offered radiotherapy with a radiosensitiser over radiotherapy alone in suitable patients. Three main regimens are commonly utilised in the UK: 43/65 (65%) of participants indicated they would choose the BC2001 regimen (concurrent mitomycin C/5-FU) [22], 22% would choose GemX (gemcitabine) [23] and 12% BCON (carbogen/nicotinamide) [24]. Whilst the responses imply widespread use of radiation with a radiosensitiser, it was not universal. The panel agreed that further research was required to determine the optimal approach.

Question 9: 'Other than a cisplatin based chemotherapy regimen if the patient is suitable, what other second line agents would you use?'

Second line treatments provide median progression-free survival of around 3-4 months [4, 25], although only one phase III controlled trial is reported to date of vinflunine plus best supportive care (BSC) versus BSC alone in platinum-refractory disease, with no benefit in the primary endpoint (overall survival in the intent to treat population) [26]. Responses indicated that 42/47 (89%) of participants would choose single agent paclitaxel. The NICE

guideline recommends consideration of second line cisplatin-based chemotherapy in suitable patients, and in those not suitable, consideration of paclitaxel combined with carboplatin or gemcitabine. The panel felt that further research was warranted. Of note, the recent UK academic study, PLUTO, incorporated paclitaxel as the control arm in comparison to pazopanib in the second line setting. Despite early termination due to futility, it provided information on single agent paclitaxel in this setting, with an overall survival of 8.0 months and median PFS of 3.2 months [27].

Conclusions

Mortality remains high in patients with MIBC and outcomes for advanced/metastatic disease remain poor. Furthermore, both bladder cancer and its treatments impact on quality of life. The NICE bladder cancer guideline was developed to clarify acceptable standards and address variation within NHS practice, so that equitable access to a consistent care standard would improve patient outcomes and satisfaction. Despite the obvious limitations of the data presented here , including selection bias of conference attendees compared to the wider community, we do feel that they provide an indication of practice patterns in the UK.

In conclusion, we consider that variation in bladder cancer management could be reduced through adoption of the NICE bladder cancer clinical guideline. Further studies are warranted to explore adoption and identify if this impacts on patient satisfaction and outcomes.

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