Urothelial carcinoma management in elderly or unfit patients#

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Urothelial carcinoma management in elderly or unfit patients☆

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these patients. The delegates discussed potential therapies, from neoadjuvant treatment to combinations or sequential regimens, maintenance therapy up to second-line management, and future treatment opportunities that could improve on current patient outcomes. Molecular specificities and future perspectives of UC were also discussed. Each individual topic of the meeting is outlined in the chapters below.

2. Defining 'difficult-to-treat patients' with UC
Maria De Santis, United Kingdom

2.1. Bladder cancer is a disease of the elderly

In the European Union, there were 118,365 new bladder cancer cases in 2012 (>500,000 worldwide), with a prevalence of 389,287 cases, and 39,522 deaths. Bladder cancer incidence peaks around the 7th decade (from the age of 60), and about 20% of patients are aged >80 years. The disease is the 4th most common cancer in males and the 15th in females [1]. Bladder cancer treatment is on a course to becoming an enormous challenge in the context of an increasingly ageing population.

Overall, the fastest growing population segment is that aged 80 years or older, which has increased from 13.8 million in 1950 to 69.2 million in 2000; it is expected to further rise to 379.0 million by 2050 [2]. Due to increased life expectancy and improved diagnostic techniques, cancers are more frequently diagnosed, resulting in higher incidence and prevalence rates. Consequently, more elderly patients will require cancer treatment.

Evidence-based guidelines recommend radical cystectomy (RC) for patients with stage II muscle-invasive bladder cancer (MIBC). However, according to the Surveillance, Epidemiology,

1. Introduction

Strategies to improve cancer care in the field of urothelial carcinoma (UC) in the elderly or in patients unfit to receive cisplatin treatment are urgently needed. This effort requires multidisciplinary collaboration to provide the best care for these patients.

An international multidisciplinary summit was held in Geneva on April 11th 2015 to discuss unmet medical needs in urothelial cancer. Key topics covered in the meeting included defining difficult-to-treat UC patients and the challenges encountered with both surgical and systemic treatment in

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and End Results database, only 21% of 3262 patients over the age of 65 underwent RC [3]. Older age at diagnosis and higher comorbidity were associated with decreased odds of receiving cystectomy, even if overall survival (OS) was better for those who underwent cystectomy compared with those who received alternative treatments (chemotherapy and/or radiation) [3]. Similarly, according to the U.S. National Cancer Data Base, out of 28,691 patients with clinical T2—T4a, N0—3 MIBC, no potentially curative therapy was delivered to 47.5% of patients. Use of RC declined dramatically with advancing age [4]. Thus, guideline-recommended RC is underused for patients with MIBC, particularly in elderly patients. The reasons that make bladder cancer unresectable or inoperable are either related to the tumour itself or to the patient. First, extensive local tumours (stage T4) might be technically inoperable; the option of shrinking the tumour with chemotherapy may be considered. Second, inoperability may be due to patient age or comorbidities (renal function impairment, cardiovascular disease, etc.). Other potential factors defining cystectomy candidates include functional (physical) status, adequacy of social support and psychological state, nutritional status, cognitive status, economic and environmental status [5].

In the context of the overall ageing population and the expected increase in incidence of invasive cancer in patients above the age of 65 years [6], comorbidities in elderly patients associated with prognostic implications must be taken into account by treating physicians. In uro-oncology, age-related physiological changes and comorbidities affect treatment choices and outcomes. Comorbidities in the bladder cancer population include renal function impairment, cardiovascular disease, neuropathy and hearing loss. Cardiovascular disease and chronic kidney disease (CKD) are more prevalent in the elderly (>65 years) [7—9]. In addition, 10—25% of individuals over the age of 65 are characterised as frail [10]. Older and 'unfit' bladder cancer patients are frequently underrepresented in clinical trials [11—13]. Importantly, not all individuals over the age of 65 are 'elderly.' A distinction between chronological and functional age must be made. Fit 70-year-olds with adequate renal function tolerate cisplatin-based chemotherapy as well as their younger counterparts and achieve comparable clinical outcomes [14]. Patients should be routinely categorised according to their physiological age in order to gauge whether elderly bladder cancer patients are fit enough to receive cisplatin, which forms the backbone of standard chemotherapeutic treatment.

2.2. Geriatric screening tools

Elderly cancer patients are a heterogeneous group with respect to overall health status, due to differences in comorbidities, functional status, geriatric syndromes and socioeconomic aspects. Although it is not standard, the comprehensive geriatric assessment (CGA) is recommended for routine use in the older patient population with cancer by several societies, including the International Society of Geriatric Oncology [15,16] and the National Comprehensive Cancer Network [17]. The CGA can distinguish fit patients from vulnerable or frail patients more precisely than physician's evaluations [18], in order to provide an estimate of

physiological age and improve anti-cancer treatment. However, because the CGA is a resource-consuming process that is not necessary in all patients, several geriatric screening tools have been developed to identify elderly cancer patients who would benefit from a CGA and multidisciplinary approach (reviewed in [15]). With the Flemish version of the Triage Risk Screening Tool and Vulnerable Elders Survey-13, the G-8 geriatric screening tool is one of the most studied tools, and has the highest sensitivity [15]. The G-8 total score ranges from 0—17, with a cut-off value of 14 (14 and above being favourable, and <14 indicating impairment, which requires CGA). The vast majority of users (98.7%) complete the test in less than 10 min (Table 1) [19].

Thus, a treatment algorithm can be derived, based on G-8 screening scores (Fig. 1). 'Fit' patients are those with a score of 14 and above and they require no geriatric assessment. 'Vulnerable' and 'frail' patients are those with a score below 14 and require geriatric assessment. In the case of 'vulnerable' patients, geriatric interventions can reverse various comorbidities such as abnormal activities of daily living (ADL) grades I or II, malnutrition, depression, or cumulative illness rating scale for geriatrics (CISR-G) grades I or II. 'Frail' patients are those for whom geriatric interventions cannot reverse comorbidities, such as abnormal ADL $\geq$3, severe malnutrition, cognitive impairment, CISR-G grades III or IV [19].

In cancer patients as a whole, it is becoming increasingly clear that treatment should be adapted to health status. On the one hand, 'fit' patients should receive the same standard treatment as younger patients, corresponding to approximately 50% of men aged 70—75 years and about 25% of men aged 80—85 years. 'Vulnerable' patients require geriatric intervention followed by standard treatment. On the other hand, 'frail' patients should receive geriatric intervention followed by adapted or palliative treatment, and those who are 'too sick' should receive palliative treatment only [20].

2.3. Conclusions

Performing a geriatric approach as part of a collaborative multidisciplinary effort is simply equivalent to good medicine. It is important to invest time in the care of elderly patients, in order to ultimately save time, provide better treatment and quality of life for these patients. Strategies to improve cancer care in the elderly are urgently needed.

3. Limitations of local treatment and alternative options in invasive bladder tumours
Nicolas Mottet, France

3.1. Local treatment: standard of care

The standard or care in MIBC is neoadjuvant chemotherapy followed by RC and pelvic lymph node dissection (PLND). Neoadjuvant chemotherapy is recommended for T2—T4a, cN0M0 bladder cancer, and should always be cisplatin-based combination therapy. Neoadjuvant chemotherapy is not recommended in patients who are ineligible for cisplatin-based combination chemotherapy. Surgical intervention or multimodality treatments are the preferred curative therapeutic

Table 1 – The G-8 questionnaire [19].

		Items	Possible responses (score)
A		Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake
B		Weight loss during the last 3 months?	0 = weight loss >3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss
C		Mobility?	0 = bed or chair bound 1 = able to get out of bed/chair but does not go out 2 = goes out
E		Neuropsychological problems?	0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems
F		BMI? (weight in kg)/(height in m^2)	0 = BMI <19 1 = BMI 19–<21 2 = BMI 21–<23 3 = BMI $\geq$23
H		Takes more than three prescription drugs per day?	0 = yes 1 = no
P		In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good 0.5 = does not know 1.0 = as good 2.0 = better
	Age		0: >85 1: 80–85 2: <80
	Total score		0–17

BMI, body mass index.
Reproduced from Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012;23:2166–72. With permission from Oxford University Press.

approaches, as they are more effective than radiotherapy (RT) alone. Multimodality treatment could be offered as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option [21]. Stratifying elderly patients according to their risk–benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimise treatment outcomes. The decision regarding bladder-sparing or RC in elderly/geriatric patients with MIBC should be based on tumour stage and comorbidity best quantified by a validated score [21] and patient's wishes, and not on the patient's age.
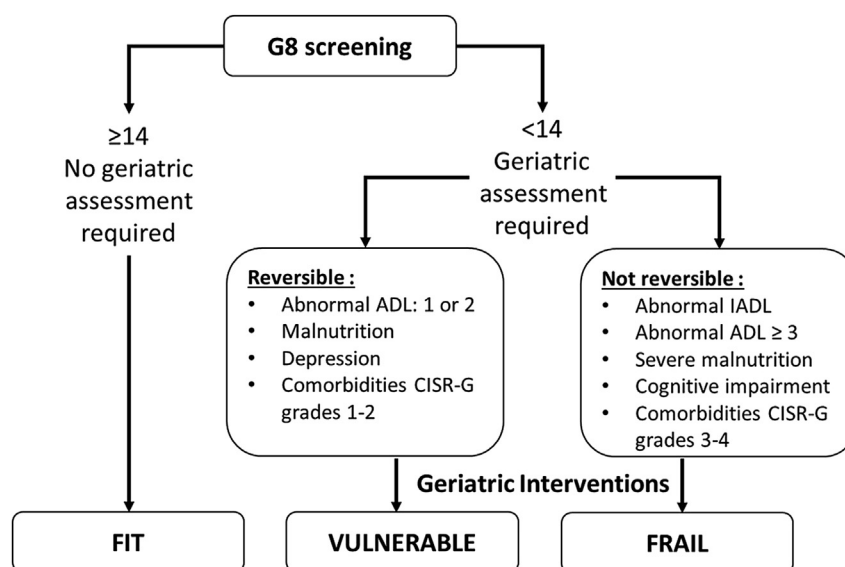

Fig. 1 – The G-8 geriatric screening tool (based on [19]). ADL, activities of daily living; CISR-G, cumulative illness rating scale for geriatrics; IADL, instrumental activities of daily living.

3.2.   Cystectomy

3.2.1.   Undertreatment of MIBC

Evidence-based guidelines recommend RC for patients with MIBC, but many patients receive alternative therapies, such as chemotherapy or radiation. A U.S. National Cancer Database study found that potentially curative aggressive therapy (i.e. radical or partial cystectomy or definitive radiation/chemo-radiotherapy [CRT, total dose $\geq$50 Gy]) was only delivered to 52.5% of patients, and use of aggressive therapy significantly decreased with advancing age (Fig. 2) [4].

Other studies have shown that cystectomy is underused in senior adults, including analyses stratifying patients by T stage [22,23]. Further, a study on bladder cancer patterns of care observed that cystectomy for muscle-invasive disease was influenced by patient age and geographic region and not by comorbidities [24].

3.2.2.   Survival data

Even though cystectomy is underused in MIBC, it is associated with better survival, independently of age, socio-economic status and serious comorbidity [25—27]. Tumour stage and number of lymph nodes removed have an impact on specific survival.

Therefore, even if older patients have a higher American Society of Anesthesiologists score, and receive less adjuvant treatment, they should not be denied RC if they are deemed fit to undergo surgery [26,27]. Studies confirm that a considerable proportion of elderly patients benefit from RC with curative intent. Of note, postoperative outcomes after RC depend on surgeon experience and case load [28].

3.3.   Neoadjuvant chemotherapy

A systematic review and meta-analysis assessed the effect of neoadjuvant chemotherapy in the treatment of patients with invasive bladder cancer. Based on 11 trials involving 3005 patients, a significant survival benefit associated with cisplatin-based combination chemotherapy (hazard ratio [HR] = 0.86, 95% confidence interval [CI] 0.77—0.95, p = 0.003) was observed, equivalent to a 5% absolute improvement in survival at 5 years. However, there was not sufficient evidence

to reliably determine the effect of single-agent cisplatin on survival [29].

A Medical Research Council/European Organisation for Research and Treatment of Cancer (MRC/EORTC) trial presented the long-term results (median follow-up 8 years) of the international multicentre randomised trial that investigated the use of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy in patients with MIBC treated by cystectomy and/or RT (of note, 17% were older than 70 years). Results showed a statistically significant 16% reduction in the risk of death (HR, 0.84; 95% CI, 0.72—0.99; p = 0.037, corresponding to an increase in 10-year survival from 30—36%) after CMV. In MIBC, neoadjuvant chemotherapy followed by definitive local therapy should be viewed as state of the art, compared with cystectomy or RT alone [30].

3.4.   Adjuvant chemotherapy

The role of postoperative adjuvant cisplatin-based chemotherapy compared with control (surgery alone) in the management of MIBC has been assessed in a meta-analysis involving 945 patients from nine randomised controlled trials (RCTs). For OS, the pooled HR across all nine trials was 0.77 (95% CI, 0.59—0.99; p = 0.049) [31].

After stratification of studies by nodal involvement, the HR for disease-free survival (DFS) associated with adjuvant cisplatin-based chemotherapy in studies where more than 50% of patients had pN+ was 0.39 (95% CI, 0.28—0.54), compared with an HR of 0.89 (95% CI, 0.69—1.15) when less than 50% of patients were pN+. Thus, according to this review, postoperative adjuvant cisplatin-based chemotherapy mainly benefits patients with nodal involvement. Furthermore adjuvant chemotherapy will never be able to compensate for poor surgical procedure, such as omitting the extended lymph node dissection (LND) [32].

The EORTC 30994 study compared immediate versus deferred cisplatin-based combination chemotherapy after RC in patients with pT3—pT4 or N+ M0 UC of the bladder. In total, 284 (out of 660 planned) patients were randomly assigned (141 to immediate treatment and 143 to deferred treatment), and after a median follow-up of 7 years, 47% of patients in the immediate treatment group had died compared with 57% in the deferred treatment group. No significant improvement in
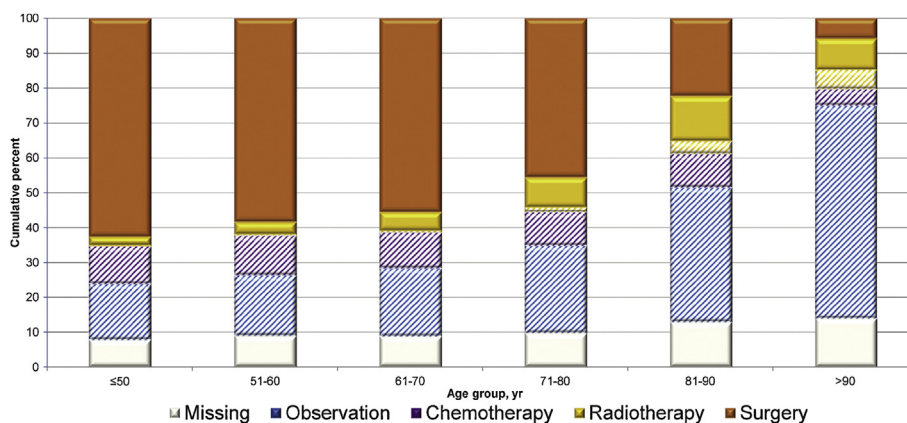

Fig. 2 — Distribution of primary therapies received by MIBC patients by age group [4]. Reproduced with permission. © European Association of Urology 2012.

OS was noted with immediate treatment when compared with deferred treatment [33]. However, these results are underpowered and still inconclusive, while suggesting a survival benefit only in node-negative patients. Therefore, no formal conclusion can be made regarding which patients benefit the most from adjuvant chemotherapy.

3.5. CRT with transurethral resection of the bladder

Radiotherapy is an alternative to cystectomy in MIBC patients. Numerous phase I/II studies have shown that CRT with transurethral resection of the bladder (TURB) is feasible and safe. Three phase III studies have demonstrated a benefit in terms of local control compared to RT alone: (i) RT versus RT + cisplatin [34]; (ii) RT versus RT + nicotinamide/carbogen [35]; (iii) RT versus RT + fluorouracil/mitomycin C [36]. The latter randomly assigned 360 MIBC patients with a median age of 72 years. At 2 years, the rates of locoregional DFS were 67% (95% CI, 59–74) in the CRT group and 54% (95% CI, 46–62) in the RT group. Five-year OS rates were 48% (95% CI, 40–55) in the CRT group and 35% (95% CI, 28–43) in the RT group (HR, 0.82; 95% CI, 0.63–1.09; $p = 0.16$).

A combined analysis of six prospective Radiation Therapy Oncology Group (RTOG) protocols evaluated bladder-preserving combined-modality therapy (CMT, all of which included cisplatin) in 468 MIBC patients (median age 66 years [range, 34–93 years, 36% were >70 years], clinical T stage T2–T4a). With a median follow-up of 4.3 years among all patients and 7.8 years among survivors (n = 205), the 5- and 10-year OS rates were 57% and 36%, respectively, and the 5- and 10-year disease-specific survival (DSS) rates were 71% and 65%, respectively. This pooled analysis of multicentre, prospective RTOG bladder-preserving CMT protocols suggests long-term DSS comparable to modern immediate cystectomy studies, for patients with similarly staged MIBC [37].

Additional reports from multiple institutional and cooperative group studies have shown that this approach is safe and effective, with OS rates similar to RC in well-selected patients [38,39]. The best cancers eligible for bladder preservation are those with low-volume T2 disease without hydronephrosis or extensive carcinoma in situ [39] and treated initially with a thorough TURB (as complete as possible). Thus, concomitant CRT is emerging as an attractive alternative for bladder preservation in selected MIBC patients, provided, patients be fit enough to receive the chemotherapy drugs.

In order to address whether cystectomy is better than external-beam radiotherapy, the survival benefit achieved with RC was compared with ERBT in patients with MIBC stratified by age. Those who underwent RC had an OS advantage in all age groups, except for octogenarians (18 versus 15 months). Patients above the age of 80 who receive RC with a limited PLND or RC alone showed little (16 versus 15 months) or no survival benefit. However, DSS was significantly higher in patients who underwent RC, including octogenarians. Even if this comparison is limited by its retrospective nature, it once again highlights that RC is effective, provided it is well done and includes a real lymphadenectomy [40].

In the MRC/EORTC trial that presented the long-term results of CMV chemotherapy in 976 MIBC patients treated by cystectomy and/or RT [30], there was no evidence that neo-adjuvant CMV was more or less effective when combined with either RT or cystectomy. For locoregional DFS, there was some evidence of a greater impact with CMV over no CMV given before cystectomy than the same chemotherapy given before RT. However, this comparison is limited, as the patient groups cannot be compared due to differences in patient and tumour characteristics (tumour stage, N0 nodal status, and performance status [PS]).

In summary, CRT with TURB results in optimal outcomes, provided the tumour is a single lesion T2, complete TURB is performed, there is no hydronephrosis or tumour invasion into prostate stroma, the patient has a well functioning bladder, and no carcinoma in situ. A formal efficacy comparison between this bladder-sparing approach and a RC is still lacking.

3.6. TURB alone

A Spanish study analysed the long-term results of an aggressive TURB for MIBC treatment in patients who were biopsied in the deep muscle layer of the tumour bed. A comparison to a control group of 76 patients with invasive pathological stage pT2–3a, N0-3 bladder cancer treated with RC was performed. At 5 and 10 years of follow-up, cause-specific survival rates were 80.5% and 74.5%, respectively. No significant difference was noted in terms of cause-specific survival with respect to the control group. For patients with invasive bladder cancer, radical TURB might be an option when the tumour is clinically limited to the muscular layer and when all biopsies of the periphery and depth of the tumour bed show muscular tissue negative for tumour cells [41].

Another study determined the 10-year outcome of MIBC patients treated with TURB alone. Of 432 patients (tumour stage ≥T2, N0, M0), 151 had a restaging TUR of the primary tumour site showing no (T0) or only non-muscle-invasive (T1) residual tumour. 52 patients opted for immediate RC, while 99 chose a bladder-sparing approach. The 10-year DSS was 76% of 99 patients who accepted to receive TURB as definitive therapy (57% with bladder preserved) compared with 71% of 52 patients who had immediate cystectomy ($p = 0.3$). The study suggested that radical TURB is a successful bladder-sparing therapeutic strategy in selected patients who have no residual tumour on a repeat extended resection of the primary tumour [42].

3.7. Partial cystectomy

There is very little evidence on partial cystectomy in MIBC patients. The most recently published study was a retrospective analysis that included 101 patients followed-up for a median of 53 months [43]. Multivariate analysis showed that prior history of UC was associated with a decrease of both cancer-specific survival (CSS) and recurrence-free survival (RFS), and was weakly associated with OS; while lymphovascular invasion (LVI) and ureteral reimplantation were associated with a decreased OS, CSS, and RFS.

An earlier retrospective study in 58 patients who had undergone partial cystectomy with LND reported an overall 5-year survival of 69% with a mean follow-up of 33 months. Of these patients, 74% were alive with an intact bladder, and

Table 2 — Hypofractionation palliative radiotherapy studies.

Reference	N	Treatment	Approach	Patient characteristics
Turgeon, 2014 (retrospective) [48]	24	Hypofractionated intensity modulated RT (50 Gy in 20 fractions) with concomitant weekly radiosensitising chemotherapy	Curative, QoL	Elderly (>70 years), T2—T3N0M0
Lacarriere, 2013 (retrospective) [49]	32	Haemostatic radiation therapy: 2 schedules: 1) 30 Gy in 10 fractions over 2 weeks (13 patients with PS < 2) 2) hypofractionated regimen: 20 Gy in 5 fractions over 1 week (19 patients with PS > 2)	Palliative-care, haematuria related to bladder cancer	'Unfit' for surgery, gross haematuria from advanced bladder cancer (G3)
Kouloulias, 2013 (prospective) [50]	58	Weekly hypofractionated 3DCRT 36 Gy in 6 weekly fractions	Symptom palliation	Elderly (>75 years), PS <70%, cT1—2N0
Zygogianni, 2013 (prospective) [51]	43	Weekly hypofractionated RT (total dose: 36 Gy in 6 fractions)	Safety, symptom palliation	Elderly, poor PS or unfit for surgery, symptomatic (daily pain on urination), T2—T3

PS, performance status; QoL, quality of life; RT, radiotherapy.

55% had been continuously disease-free with an intact bladder. On multivariate analysis, concomitant carcinoma *in situ* (odds ratio [OR] 7.05, $p = 0.004$) and lymph node involvement (OR 4.38, $p = 0.031$) were predictors of advanced recurrence [44]. However, unlike reports by Dandekar *et al*. and Malkowicz *et al*., this study did not comment on lesion localisation [45,46].

Recent population-based series and single institution cohorts have found that partial cystectomy did not compromise survival when compared to RC in very selected patients with organ-confined disease, a single limited lesion without carcinoma *in situ*, N0, and mainly located at the bladder dome. Additional research is needed to clarify patient selection and outcomes [47].

3.8. Palliative radiotherapy: hypofractionation

Reasons for being unfit and for qualifying to receive palliative treatment alone include age, comorbidity, palliation of symptoms, and short life expectancy. In these situations, palliation is the priority. Hypofractionation might represent an attractive modality, avoiding too many journeys to the radiotherapy department and the associated fatigue (Table 2).

3.9. Conclusions

The standard treatment approach in MIBC is neoadjuvant chemotherapy followed by RC and PLND. Age is not a limitation for optimal treatment, whereas comorbidity and individual life expectancy are. There are effective alternative treatments in the form of bladder-sparing strategies, of partial surgery (super selection) and combined CRT (with or without cisplatin). Finally, palliative RT is proposed to very unfit patients.

4. Challenging patient profiles and 'unfit' patients in advanced UC
Maria De Santis, United Kingdom

4.1. Standard chemotherapy

The standard of care for advanced and metastatic UC is cisplatin-based combination chemotherapy. Long-term OS and progression-free survival (PFS) after treatment with gemcitabine plus cisplatin (GC) or methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) have been shown to be similar, as were response rates. Only toxicity was in favour of GC [52,53] (Table 3).

Cisplatin has also been compared with carboplatin in cisplatin-eligible UC patients (Table 4). The carboplatin combinations of all trials resulted in lower complete response (CR) rates and shorter OS. A comparative effectiveness study of 286 patients from four randomised trials confirmed that cisplatin-based chemotherapy was associated with a significantly higher likelihood of achieving a CR (risk ratio [RR] = 3.54; 95% confidence interval [CI] 1.48—8.49, $p = 0.005$) and overall response rate (ORR) (RR = 1.34; 95% CI 1.04—1.71, $p = 0.02$) [55]. Thus, the standard first-line chemotherapy for UC should be cisplatin-based, which provides 13—15 months of OS.

Table 3 – Long-term follow-up data of cisplatin combination chemotherapy.

Author Treatment arm	N (ITT)	Median follow-up (years)	Median survival (months)	5-year (%)
Sternberg, 2006 [54]	263	7.3	14.9	
MVAC	129		15.1	13.5
HD-MVAC	134			21.8
von der Maase, 2005 [53]	405	>5		
MVAC	203		14.0	15.3
GC	202		15.2	13.0
Visceral metastases				6.8
No visceral metastases				21.9

GC, gemcitabine plus cisplatin; HD, high dose intensity; ITT, intention to treat; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.

The use of cisplatin is limited in daily practice. Only 35.9% of 298 patients presenting with advanced UC to 42 community cancer centres were treated with cisplatin [59]. This percentage was similar for 1077 'real world' patients treated in 23 centres of excellence [60] (Table 5). A more recent published study on patterns of practice in 327 advanced UC patients in Greece reported that 55% did not receive cisplatin-based therapy [61]. Given that the majority of patients may not be eligible to receive cisplatin-based chemotherapy, this population has a significant unmet need.

4.2. 'Unfit' for cisplatin

There is so far no established standard chemotherapy in patients who are 'unfit' to receive cisplatin, even though more than 50% of UC patients are not eligible for standard cisplatin-based chemotherapy [20,62–64]. As discussed, comorbidities and age mean that elderly patients are often excluded or under-represented in clinical trials. It is, therefore, not clear whether dosages investigated in clinical trials are realistic or safe in the elderly and comorbid population.

In the first randomised phase III trial for cisplatin-ineligible patients conducted by the EORTC, patients were defined as

Table 4 – Randomised phase II studies of cisplatin versus carboplatin in cisplatin-eligible UC patients.

Regimens	CR (%)	OS (months)	Reference
MVAC versus MVECa	25	13	Petrioli,
	11	9.5	1996 [56]
MVAC versus Carbo/MV	13	16	Bellmunt,
	0	9	1997 [57]
GC versus Carbo/gem	14.5	12.8	Dogliotti,
	1.8	9.8	2007 [58]

Carbo/gem, carboplatin, gemcitabine; Carbo/MV, carboplatin, methotrexate, vinblastine; CR, complete response; GC, gemcitabine plus cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; MVECa, methotrexate, vinblastine, epirubicin and carboplatin; OS, overall survival; UC, urothelial carcinoma.

Table 5 – First-line chemotherapy in advanced/ metastatic UC in routine practice.

	Community database [59] N = 298	RISC group [60] N = 1077
No chemotherapy	24%	30%
Cisplatin-based	36%	36%
Carboplatin-based	27%	20%
Non-platinum regimen	8%	14% (1 agent: 11%)
Data non-available	5%	–

RISC, Retrospective International Study of Invasive/Advanced Cancer of the Urothelium; UC, urothelial carcinoma.

unfit to receive cisplatin if their creatinine clearance (CrCl) was <60 ml/min and/or the ECOG PS was 2 [62,65,66]. In 2011, a consensus conference provided a more uniform description of patients unfit for cisplatin for inclusion in clinical trials [65] (Table 6).

Performance status in patients unfit to receive cisplatin must be taken into account with functional status, or with other assessment tools (e.g. CGA). Since no standard chemotherapy has been established for this patient group, the development of well tolerated single-agent therapy or cisplatin-free combination regimens is a priority in view of the substantial number of patients who are not eligible for cisplatin.

4.3. Treatment of bladder cancer in the elderly

The main challenge when treating bladder cancer in the elderly is the use of cisplatin, whose pharmacokinetic properties principally rely on renal elimination [67]. With increasing age, comorbidities increase and renal function decreases [68]. Therefore, serum creatinine will be cleared more slowly in older patients, and will not provide an accurate reflection of renal function. Renal dysfunction is common in oncology patients and many chemotherapy agents, including cisplatin, are nephrotoxic. Renal function should be evaluated before every treatment course in all cancer patients, using either the Cockcroft-Gault or the Modification of the Diet in Renal Disease (MDRD) formulae, including in patients with normal serum creatinine. The use of additional nephrotoxic agents should be avoided whenever possible. Reduced or split-

Table 6 – Eligibility criteria for enrolling metastatic UC patients 'unfit' for cisplatin-based chemotherapy in clinical trials [65].

Eligibility criteria (at least one of the following)

1. WHO or ECOG PS 2 or Karnofsky PS of 60–70%
2. CrCl (calculated or measured) <60 ml/min
3. CTCAE v4 grade ≥II audiometric hearing loss
4. CTCAE v4 grade ≥II peripheral neuropathy
5. NYHA class III heart failure

CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status; WHO, World Health Organization; UC, urothelial carcinoma.
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Table 7 — Outcomes of patients who refused cystectomy after receiving neoadjuvant chemotherapy for MIBC.			
	Herr, 2008 [71]	Sternberg, 2003 [72]	Meyer, 2014 [73]
CR after neoadjuvant MVAC (cT0)	N = 63	N = 37	N = 25
5-year survival DSS	64%	68%	88%
Intact bladder	54%	51%	72%
Relapse in bladder	64%	35%	52%
Muscle invasive			28%
Non-muscle invasive			24%
Relapse metastatic	NR	24%	—
Additional mortality	30%	32%	—
Alive with bladder intact	NR	38%	—

CR, complete response; DSS, disease-specific survival; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NR, not reported; MIBC, muscle-invasive bladder cancer.

dose cisplatin, or reduced infusion rates, should be administered to avoid excessive toxicity in elderly patients. It is also important to monitor hydration. Moreover, patients above 70 years of age are frequently diagnosed with CKD and have more prevalent comorbidities (hypertension, diabetes, stroke and ischaemic heart disease) than patients without CKD [69].

In addition, the occurrence of neuropathy is associated with cumulative doses of cisplatin and taxanes. Age is also a risk factor for developing peripheral neuropathies induced by chemotherapy [70].

4.4. Bladder preservation after chemotherapy

According to the European Association of Urology guidelines, chemotherapy alone is not recommended for the treatment of the primary tumour [21]. The main reason is the high incidence of relapse in the bladder, with added mortality. The outcomes of patients who did not undergo cystectomy after having received neoadjuvant chemotherapy for MIBC are summarised in Table 7. Clinically complete responders after neoadjuvant chemotherapy for MIBC may have the option to retain the bladder with durable survival, but the added risks and deviation from the guidelines must be openly discussed.

Table 9 — EORTC 30986 study: first-line therapy in bladder cancer patients unfit for cisplatin-based chemotherapy [78].				
Regimen	ORR (%) confirmed (%)	OS (months)	Severe acute toxicity (%)	Toxic death (%)
GCa	41.2 36.1	9.3	9.3	1.7
M-CAVI	30.3 21.0	8.1	21.2	3.4

GCa, gemcitabine/carboplatin; M-CAVI, methotrexate, carboplatin, and vinblastine; ORR, overall response rate; OS, overall survival.

4.5. First-line treatments in unfit patients

Various combination regimens in patients unfit for cisplatin-based chemotherapy show an ORR of at best 30—40% and a median OS of 8—10 months [74—82]. Single arm studies with more positively selected patients, in particular those having a solitary kidney as single inclusion criterion for cisplatin ineligibility, reported longer OS with up to 15 months (Table 8) [82—85].

The EORTC 30986 study is the only available phase III trial that compared two carboplatin-containing first-line chemotherapy regimens (methotrexate, carboplatin, and vinblastine [M-CAVI] versus gemcitabine/carboplatin [GCa]) in clearly defined cisplatin-ineligible patients with advanced UC [78] (Table 9).

No significant differences in OS and PFS were observed, but a significant difference for confirmed RR was noted in favour of GCa (36.1% versus 21%, $p = 0.01$) (Table 9). Fewer adverse events (AEs) were reported with GCa, but there were still grade III/IV AEs (neutropenia 52.5%; thrombocytopenia 48.3%; febrile neutropenia [FN] 4.2%). In patients with both PS 2 and impaired renal function, increased severe acute toxicities (SAT, defined as death, grade IV thrombocytopenia with bleeding, grade III/IV renal toxicity, FN or mucositis), low response rate and a shorter OS were reported. This led to the recommendation against combination chemotherapy in such patients and in favour of single-agent therapy or best supportive care (BSC). The EORTC 30986 study also reported low efficacy and elevated SAT in patients negatively selected according to known prognostic factors [78,86].

Table 8 — Selected first-line treatment studies in unfit patients.					
Author, year	Phase, N	Patient profile	ORR (%)	Median PFS (months)	Median OS (months)
Doxorubicin—gemcitabine → paclitaxel—carboplatin					
Galsky, 2007 [83]	II; 25	CrCl <60 ml/min and/or prior nephrectomy	56	NR	15
Bevacizumab + gemcitabine—carboplatin → bevacizumab					
Balar, 2013 [84]	II; 51	CrCl <60 ml/min and/or solitary kidney and/or KPS 60—70%	43	6.5	13.9
Gemcitabine					
Culine, 2011 [82]	R II; 21	CrCl 30—60 ml/min and/or PS 2	43	3.8	5.4
Sunitinib					
Bellmunt, 2011 [85]	II; 38	CrCl 30—60 ml/min (PS 0—1)	8	4.8	8.1

KPS, Karnofsky performance status; PFS, progression-free survival; ORR, overall response rate; CrCl, creatinine clearance; OS, overall survival; NR, not reported; UC, urothelial carcinoma.

Two additional phase II randomised trials evaluating vinflunine first-line treatment in cisplatin-unfit patients are ongoing. Vinflunine is a novel anti-cancer agent approved for advanced or metastatic UC previously treated with a platinum-based regimen. The Northern Urology Cooperative Oncology Group 1 trial is comparing vinflunine plus gemcitabine versus GCa. The JASINT open-label, multicentre, international randomised phase II study is assessing the combination of gemcitabine or carboplatin with vinflunine [87]. Preliminary safety results showed more haematological grade III/IV AEs in the carboplatin arm [87]. Clinical outcomes, response rates and survival are expected to be published soon.

4.6.   Second-line treatment options

Choice of second-line therapy depends on time to progression after first-line treatment, renal function, and PS [21]. Several traditional cytotoxic agents as well as novel targeted agents have been tested in the second-line setting. Response rates of taxanes (weekly paclitaxel, docetaxel, nab-paclitaxel), oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have been modest (up to 28%) in small phase II trials [88,89]. Gemcitabine has shown very good response rates, but most patients already receive this drug during first-line treatment [90]. Paclitaxel/gemcitabine studies have shown response rates of up to 60%, but randomised phase III trials evaluating this combination in the second-line setting have not included an adequate comparator arm [91–93].

Several single-agent phase II studies have tested targeted therapies in the second-line setting, but none have shown substantial activity. Trials are also testing targeted agents combined with a cytotoxic drug (paclitaxel + cetuximab or docetaxel + vandetanib), but the combinations exacerbated toxicity, and no synergistic or additive effects were reported [94,95]. More recent attempts at combining targeted agents with cytotoxic drugs have been more encouraging (docetaxel + ramucirumab versus docetaxel), based on the results of a phase II trial, although toxicity was increased in the combination arm [96]. Another single-arm phase II study which combined pazopanib with paclitaxel reported good ORR values but significant myelosuppression [97].

A phase III trial compared long-term OS of patients with advanced UC treated with vinflunine plus BSC or BSC alone, after failure of platinum-based chemotherapy [98]. The study showed a >2 month survival difference in favour of the vinflunine arm, which was maintained after >3.5 years' follow-up. With vinflunine, the risk of death was reduced by 22%. There were also some long-term survivors in the vinflunine arm (at 40 months follow-up cut off) [98]. For second-line treatment of advanced or metastatic UC, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment [21]. Adverse prognostic factors validated in vinflunine studies for pretreated patients include liver metastases, Hb <10 g/dl, and ECOG PS ≥1 [99,100]. Available prospective and retrospective data on vinflunine use in routine practice for unselected populations include 422 patients from 87 centres (Table 10).

These recent data from European phase IV studies performed in real life confirm the efficacy of vinflunine, even in patients with adverse prognostic factors [101]. Each of these studies report a median OS that exceeds the 6.9 months reported in the phase III trial [98]. In real life, vinflunine was safe with manageable toxicity (Table 11). Myelosuppression is usually managed with granulocyte colony-stimulating factor in these patients, particularly if dose modifications are insufficient [105].

Vinflunine is especially interesting in the context of special patient populations, including those with renal or hepatic impairment, and elderly patients. Vinflunine has been shown to be safe in patients with a CrCl as low as 20 ml/min [106]. These conditions are not contraindications to vinflunine use, but require dose adjustments. In the case of renal impairment, the dose needs adjusting according to CrCl values. In patients whose CrCl is ≥60 ml/min, standard vinflunine dosing of 320 mg/m^2 every 3 weeks (q3w) is recommended, or 280 mg/m^2 q3w in patients who are PS 1 or who have received prior radiotherapy. The same lower dose of 280 mg/m^2 q3w is recommended in patients whose CrCl is 40–60 ml/min, and a further reduced dose of 250 mg/m^2 q3w in patients whose CrCl is 20–40 ml/min. The large experience in the post-platinum setting, phase II and III study data, and real world experience all demonstrate that vinflunine is safe in patients with CrCl <60 ml/min. Indeed, the 'tolerance profile of vinflunine in patients with renal dysfunction was similar to that observed in patients with CrCl >60 ml/min' [106]. Vinflunine can be used in patients with hepatic impairment, provided it is not severe. Doses of 250 mg/m^2 or 200 mg/m^2 q3w are

Table 10 – Vinflunine efficacy in routine practice.					
	Germany [101]	France [101]	UK [102]	Spain [103]	Greece [104]
Patients	77	134	38	102	71
1st-line therapy	Platinum-based chemotherapy				
ECOG PS/Karnofsky	Median Karnofsky: 80	PS 0: 25%	PS 0–1: 92%	PS 0: 31%	PS 0: 24%
		PS 1: 46%	PS 2: 8%	PS 1: 61%	PS 1: 53%
		PS ≥2: 23%		PS 2: 8%	PS 2: 20%
					PS 3: 3%
Visceral involvement	60% (visceral)	57% (lung + liver)	39% (lung) 29% (liver)	29% (lung) 17% (liver)	42% (lung) 30% (liver)
Number of cycles	Average: 5	Median: 5 (1–23)	Median: 3 (1–16)	Median: 4 (1–18)	Median: 4 (1–16)
ORR (%)	23	22	32	25	16.3
DCR (%)	53	51	53	66	–

DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; PS, performance status.

Table 11 – Vinflunine safety in routine practice.

Grade III/IV adverse events	Germany (n = 77) [101]	France (n = 134) [101]	UK (n = 38) [102]	Spain (n = 102) [103]	Greece (n = 71) [104]
Haematological adverse events (% patients)					
Neutropenic infection or febrile neutropenia (%)	1	3	5	NR	NR
Neutropenia (%)	NR	17	3	13	16.3
Anaemia (%)	6	8	5	NR	4.1
Non-haematological adverse events (% patients)					
Constipation (%)	5	8	11	6	12.2
Abdominal pain (%)	NR	3	0	5	NR
Asthenia/fatigue (%)	1	21	8	NR	16.3
Vomiting (%)	3	NR	0	2	NR

NR, not reported.

recommended in patients with mild Child-Pugh Grade A and moderate (Grade B) impairment, respectively.

In addition, vinflunine is safe in elderly patients; most common AEs do not differ from those seen in younger patients. Similarly to patients with renal impairment, based on pharmacokinetic and safety data, vinflunine should be started at 280 mg/m^2 q3w in patients who are aged 75–79 years, and the dose should be lowered to 250 mg/m^2 q3w in patients aged ≥80 years who are in good shape [107]. The decision on which dose to administer depends on biological parameters. Upper age thresholds are currently not outlined in clinical trials.

4.7. Conclusions

Urothelial cancer patients are of higher median age and often present with organ impairment and comorbidities. Cisplatin-based chemotherapy is the standard first-line treatment in advanced UC. However, more than 50% of patients are not eligible for cisplatin due to age and/or renal comorbidities, meaning that alternative treatment options are needed for these patients. Medical management should consider nephrotoxicity of drugs and patients' performance status and organ function.

The first randomised phase II/III trial in 'unfit' patients showed that M-CAVI and GCa are active, with a toxicity profile in favour of GCa. Thus, in patients ineligible for cisplatin due to a single risk factor (e.g. renal function), the standard regimen is GCa. There may be a role for splitting cisplatin doses in the case of renal function impairment. Patients ineligible for cisplatin are not a uniform group, and successful outcomes of combination therapy depend on renal function, PS and the presence/absence of prognostic factors. In frail patients, recommended treatment options include carboplatin or gemcitabine monotherapy, or GCa if possible. This population is challenging because these patients are difficult to include and accrue in clinical trials.

Novel treatments and combinations with vinflunine are promising in an area of unmet need in the first-line setting in patients who are elderly or unfit to receive cisplatin. Vinflunine has a favourable toxicity profile, including in elderly patients or in patients with impaired renal function, provided that the dose is adjusted. For second-line treatment of advanced or metastatic UC, vinflunine is currently the only approved treatment option, although many trials have

evaluated traditional cytotoxic agents and combinations with targeted agents.

5. Management of upper tract UC: surgical aspects
Nicolas Mottet, France

5.1. Surgery

The standard surgical modality in UC of the upper urinary tract (UTUC) is a radical nephroureterectomy (RNU) plus LND followed by single immediate postoperative intravesical instillation (usually with mitomycin C). New data suggest that a systematic conservative approach is standard of care in selected patients (Fig. 3) [108].

Low-risk UTUC is defined by the presence of all the following factors: unifocal disease, tumour size <1 cm, low-grade cytology, low-grade ureteroscopic (URS) biopsy, and no invasive aspect on multidetector computed tomography-urography. On the other hand, high-risk UTUC is defined by the presence of either of these factors: hydronephrosis, tumour size >1 cm, high-grade cytology, high-grade URS biopsy, multifocal disease, and previous RC for bladder cancer [108].

In case of lesion suspicion upon imaging and negative or low-grade cytology, it is recommended to perform an ureteroscopy and biopsy, whereas ureteroscopy is optional in the case of positive cytology.

5.1.1. Conservative treatment (low-risk UTUC)
Techniques used in the conservative management of low-risk UTUC are as follows [108]:

- Laser should be used for endoscopic treatment
- Flexible ureteroscopy is preferable to rigid ureteroscopy: especially for renal pelvis, distal, and mid-ureter
- A percutaneous approach remains an option in low-grade tumours unsuitable for URS treatment

Conservative treatment may also be extended to (low-grade only) multifocal lesions (pelvis only) without ureteral locations or tumours <3 cm, provided they are in the pelvis and non-flat. In the future, biological markers associated with low-grade lesions may play a role in patient selection. One

unsolved issue is the role of adjuvant (mainly percutaneous) instillations in low-risk UTUC patients.

5.1.2. Lower ureter management

Conservative treatment is performed most of the time in the distal ureter, provided the approach is feasible. Endoscopic removal is recommended in low-grade, small, non-circular tumours. Complete distal ureterectomy and neocystostomy are indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely endoscopically, and for high-grade, locally-invasive (i.e. T2) tumours. Of note, the upper ureter must be normal, and kidneys must be functional [108].

5.1.3. Radical surgery (high-risk UTUC)

RNU plus LND is recommended in high-risk UTUC patients. The procedure involves removal of perinephretic fat. No difference in recurrence or cancer-specific mortality has been reported when comparing open versus laparoscopic RNU in 1249 patients from 13 international centres [109], provided that surgical principles are respected and that the urinary tract is closed.

It is essential to remove the bladder cuff in RNU. The prognostic impact of bladder cuff excision at nephroureterectomy on cancer-specific mortality was quantified in a population-based cohort of 4210 UTUC patients. In univariable and multivariable analyses, omission of bladder cuff excision increased cancer-specific mortality rates in patients with pT3N0/x, pT4N0/x, and pT(any)N1–3 UC of the renal pelvis

[110]. Unfortunately, in real practice the standard principle of RNU with systematic bladder cuff removal is not followed in about 50% of patients despite clear guidelines [109].

Intravesical recurrence after RNU is a frequent event requiring intense bladder surveillance with endoscopy. A retrospective analysis in 2681 patients treated with RNU for UTUC at 24 international institutions compared outcomes following RNU using three different methods of bladder cuff management (transvesical, extravesical, and endoscopic) [111]. Of the 2681 patients, 67.5% underwent the transvesical approach; 29.3%, the extravesical approach; and 3.2%, the endoscopic approach. There was no difference in terms of RFS, CSS, and OS among the three distal ureteral management approaches. Patients who underwent the endoscopic approach were at significantly higher risk of intravesical recurrence compared with those who underwent the transvesical ($p = 0.02$) or extravesical approaches ($p = 0.02$); the latter two groups did not differ from each other [111].

5.1.4. Nodal dissection

Nodal dissection is not necessary if pTa/1: max 2% pN+, but it is mandatory in the following instances: ≥pT2 (16% pN+); pT2 (8% pN+); pT3 (17% pN+), or pT4 (46% pN+). RNU provides local control and CSS in patients with localised UTUC. Pathologic tumour grade, T stage, LN status, tumour architecture, and LVI are important prognostic variables associated with oncologic outcomes, which could potentially be used to select patients for adjuvant systemic therapy [112].
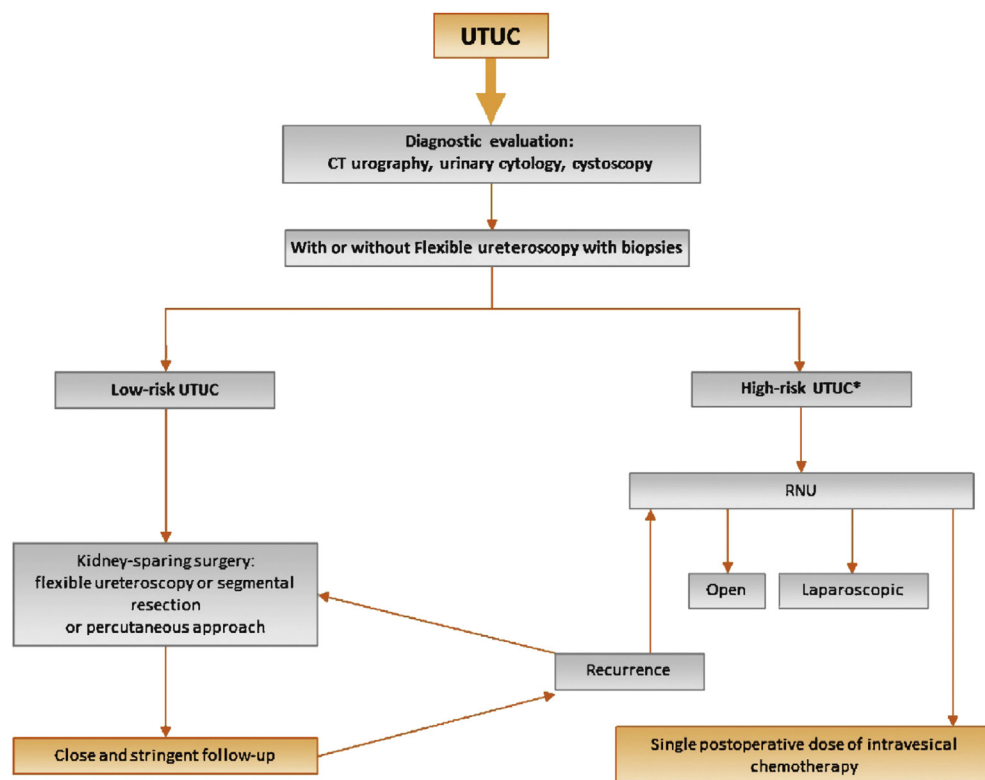

Fig. 3 – Proposed flowchart for the management of UTUC [108].*In patients with solitary kidney, consider a more conservative approach. CT, computed tomography; RNU, radical nephroureterectomy; UTUC, upper urinary tract urothelial cell carcinoma.

Having addressed when to perform nodal dissection, clear templates remain to be established to perform the procedure. This depends on lesion location and requires formal clinical validation [108] (Table 12).

5.1.5. Postoperative instillation
Guidelines for RNU in UTUC recommend postoperative instillation following surgery to avoid bladder recurrence [108]. Two studies have demonstrated that a single immediate postoperative bladder instillation dose reduces the risk of bladder tumour recurrence [113,114].

5.2. Conclusions

The main take home message in terms of UTUC surgical management is that a conservative procedure should be applied when feasible. Patients are required to have a closed urinary tract. If RNU is performed, it must include bladder cuff removal and early postoperative instillation at urethral catheter removal; nodal dissection must also be carried out in muscle-invasive lesions.

6. Molecular specificities in UC
Joaquim Bellmunt, Spain

6.1. Introduction

New options are needed for treating metastatic bladder cancer, since median survival and response rates with standard therapy (MVAC) have evolved little over the last 30 years. As discussed, superficial disease is treated with TURB plus intravesicular therapy, which includes Bacillus Calmette−Guérin (BCG), mitomycin C, or other investigational agents such as gemcitabine. Localised muscle-invasive disease is managed with cystectomy and neoadjuvant (the standard) or adjuvant chemotherapy; chemoradiation is used if a bladder-sparing approach is opted for. Metastatic disease is treated mainly with chemotherapy, and there are a wide variety of available agents whose role is well established, including cisplatin, carboplatin, or gemcitabine. Immunotherapy and targeted therapies are emerging and highly promising strategies that are awaiting confirmation for being established in this setting.

An improved understanding of molecular specificities of bladder cancer will provide new opportunities for prognostic application and personalised therapy. The sections below present an overview of the latest cancer genomics data in UC, and the potential use of tumour genetics in bladder cancer.

In the future, precision medicine and the analysis of large-scale somatic and germline genomics may impact individual patient treatment in bladder cancer and individualise patient care.

6.2. Recurrence and progression in high-grade 'superficial' bladder cancer

Approximately 21% of superficial bladder cancers progress to muscle-invasive or more advanced disease stages, and 50% of localised muscle-invasive disease progresses to metastatic disease. Although risk tables provide a prognostic tool, no molecular biomarkers accurately predict disease recurrence, progression or cancer-specific mortality [115].

A recent meta-analysis in high-grade T1 non-muscle-invasive bladder cancer assessed selection criteria for early cystectomy in these patients. The highest impact risk factor was depth of invasion (T1b/c) into lamina propria (progression: HR = 3.34, $p < 0001$; CSS: HR = 2.02, $p = 0.001$). Several other factors also predicted progression and CSS (LVI, associated clinically-isolated syndrome, non-use of BCG, tumour size >3 cm, and older age) [116].

6.3. Chemotherapy in muscle-invasive disease

As discussed, the timing of perioperative chemotherapy in MIBC patients is a subject of debate. Benefit of neoadjuvant chemotherapy is now well established, but survival benefit from adjuvant chemotherapy seems less evidence-based. An updated meta-analysis on the benefit of postoperative adjuvant cisplatin-based chemotherapy versus surgery alone in 945 patients from nine RCTs reported the following efficacy outcomes, providing evidence of a survival benefit in MIBC patients receiving adjuvant cisplatin-based chemotherapy after RC [31] (Table 13).

Larger studies of adjuvant chemotherapy from meta-analyses and retrospective cohorts show some OS benefit, but not with a high level of evidence (Table 14).

6.4. Molecular determinants of response

Several genetic UC molecular markers that predict response to chemotherapy are emerging. Whole exome sequencing on

Table 12 − Lesion location and nodal dissection.

Lesion location	Location of nodal dissection
Right pyelic lesion	Renal hilum, para, retro cave
Left pyelic lesion	Renal hilum, para-aortic
Right lumbar ureter (down to iliac vessels)	Renal hilum, para, retro cave, inter-aorticocave
Left lumbar ureter (down to iliac vessels)	Renal hilum, para-aortic
Right ureter (below iliac vessels)	Primitive external, internal obturator
Left ureter (below iliac vessels)	Primitive external, internal obturator

Table 13 − Efficacy of postoperative adjuvant cisplatin-based chemotherapy versus surgery alone in MIBC patients receiving adjuvant cisplatin-based chemotherapy after RC [31].

End-point	HR	95% CI	p Value
OS	0.77	0.59−0.99	0.049
OS in LN (+)	0.66	0.45−0.91	0.014
DFS	0.66	0.48−0.92	0.014

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LN, lymph node; MIBC, muscle-invasive bladder cancer; OS, overall survival; RC, radical cystectomy.

Table 14 − Efficacy of adjuvant chemotherapy from meta-analyses and retrospective cohorts.

Reference	Design	Total N (adjuvant chemo. n)	Level of evidence	OS HR (95% CI)
ABC, 2005 [117]	Individual patient data meta-analysis from 6 RCTs	491 (246)	2a	0.75 (0.60−0.96)
Leow, 2014 [31]	Literature-based meta-analysis from 9 RCTs	945 (475)	2a	0.77 (0.59−0.99)
Svatek, 2010 [118]	Retrospective cohort study from 11 high volume centres	3947 (932)	2c	0.85 (0.72−0.97)*
Booth, 2014	Population-based retrospective cohort	2809 (541)	2c	0.71 (0.62−0.81)
Galsky, 2015	Population-based retrospective cohort	5653 (1293)	2c	0.72 (0.65−0.80)

Cancer-specific survival. CI, confidence interval; HR, hazard ratio; OS, overall survival; RCT, randomised controlled trial.

pretreatment tumour and germline DNA from 50 patients with MIBC who received neoadjuvant cisplatin-based chemotherapy followed by cystectomy identified *ERCC2*, a nucleotide excision repair gene, as being mutated in cisplatin responders compared with non-responders [119].

Similarly, a pathologic CR to neoadjuvant chemotherapy containing platinum is a strong prognostic determinant for MIBC patients. Erb-b2 receptor tyrosine kinase 2 (*ERBB2*) mutations characterise a subgroup of MIBC with excellent response to neoadjuvant therapy [120].

A neoadjuvant clinical trial is underway to compare the clinical efficacy of GC versus MVAC and the ability of a gene expression profiling-based algorithm (CoXEN) to predict complete pathological response [121].

6.5.   Bladder-preservation as a CMT

Long-term outcomes in MIBC patients after bladder-preserving CMT were assessed in a pooled analysis of five phase II studies and one phase III study that included a total of 468 patients. With a median follow-up of 7.8 years among survivors (n = 205), the 5- and 10-year OS rates were 57% and 36%, respectively, and the 5- and 10-year DSS rates were 71% and 65%, respectively. The study demonstrated long-term outcomes comparable to modern immediate cystectomy studies. Given these long-term outcomes, bladder-preserving CMT can be considered as an alternative to RC, especially in elderly patients not well suited for surgery [37].

Protein expression of DNA damage signalling proteins in tumour samples was measured prior to radical radiotherapy or cystectomy in MIBC patients. In the RT cohort, low tumour MRE11 expression was associated with worse 3-year CSS compared with high expression, highlighting this protein as a predictive factor associated with survival following RT [122].

A report in patients with clinical stage T2−4a MIBC treated with TURB plus cisplatin-based induction and consolidation chemoradiation regimens (and RC for invasive tumour recurrence) showed variations in 3-year OS estimates depending on vascular endothelial growth factor (VEGF) expression patterns [123].

6.6.   Precision oncology

The progression towards targeted therapy in UC is underway. Some cancers are still treated with non-specific or non-targeted chemotherapy. 'Druggable' tumour-specific genetic targets are increasingly the focus of research. In other cancers,

molecular profiling has identified single drug targets such as BCR-ABL in chronic myeloid leukaemia, KRAS in colorectal cancer, or BRAF in melanoma.

So far, no molecularly targeted agents have been approved for bladder cancer treatment. Genomic alterations of anaplastic lymphoma kinase (*ALK*) have been reported in UC patients, but no association between *ALK* copy number alteration and OS, ECOG PS, or development of visceral disease was observed [124].

Bladder cancer is a molecularly heterogeneous disease. The Cancer Genome Atlas (TCGA) project reported molecular alterations in several genes involved in cell cycle regulation, chromatin regulation, and kinase signalling pathways, identifying potential therapeutic targets [125]. The TCGA findings have prompted the design of several genomic target driven trials.

6.6.1.   Cell cycle regulatory genes, signalling pathways and immunotherapy

An ongoing phase II trial is testing palbociclib (PD-0332991) in patients with metastatic UC with mutated *RB* and inactivated p16 or overexpressed CCND1 after failure of first-line chemotherapy. The trial will explore the association of molecular markers with outcomes of palbociclib response and the association between UC molecular subtypes (basal-like or luminal) with outcomes of response or resistance to palbociclib (ClinicalTrials.gov Identifier: NCT02334527).

Whole-genome sequencing was used to investigate the genetic basis of a durable remission of metastatic bladder

Table 15 − Planned interim analysis grade ≥III AEs safety results [96].

	Docetaxel (N = 44)	Docetaxel + ramucirumab (N = 46)
Haematological toxicities		
Neutropenia	36	28
Febrile neutropenia	11	20
Anaemia	5	9
Thrombocytopenia	0	7
Non-haematological toxicities		
Fatigue	11	33
Pneumonia	9	13
Sepsis	7	9
Stomatitis	0	7
Diarrhoea	2	7

AEs, adverse events.

cancer in a patient treated with everolimus, a drug that inhibits the mammalian target of rapamycin (mTOR) signalling pathway. A loss-of-function mutation was identified in tuberous sclerosis complex 1 (TSC1), a regulator of mTOR pathway activation. TSC1 mutation correlated with everolimus sensitivity [126]. As a result, several ongoing phase I/II trials are investigating the impact of PI3K/mTOR pathway genomic alterations in metastatic UC patients treated with various regimens, in order to help identify the best responding patients. In addition, fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitors are an emerging area of interest in cancer therapeutics. Proof-of-concept was recently established by two trials targeting FGFR3 in previously-treated FGFR3-mutant or translocated metastatic UC [127,128].

Studies are being designed in order to accelerate clinical drug development in UC. The Alliance MATCH-UP study aims to apply molecular findings to clinical trials by allocating drugs based on molecular screening in metastatic UC following platinum-based chemotherapy.

Finally, the programmed death-1 (PD-1) receptor/PD-1 ligand (PD-L1) pathway negatively regulates T-cell-mediated responses. The prognostic impact of PD-L1 expression was defined in UC. Results from 160 tumour samples showed that PD-L1 is widely expressed in tumour cell membrane and tumour-infiltrating mononuclear cells (TIMCs). PD-L1 expression in TIMCs was significantly associated with longer survival in patients who developed metastases [129] and received subsequent chemotherapy. Using PD1 or PD-L1 as a target, several studies have shown encouraging results with anti-PD-L1 antibodies (pembrolizumab and MPDL3280A) in UC patients with PD-L1-positive advanced tumours [130,131]. Promising long lasting responses have been seen in a selected subgroup of patients. These drugs are now undergoing testing in phase III trials versus chemotherapy, in the second-line setting.

6.7. Intrinsic subtypes in MIBC

In other diseases such as breast cancer, intrinsic subtypes are well characterised (*e.g.* luminal, HER2-positive, triple-negative) [132], each of which are associated with distinct clinical management approaches. The objective in UC has been to develop similar treatment algorithms. Based on current research, the following intrinsic subtypes and clinical features have been described in MIBC [133,134]:

- Luminal: enriched with papillary histology and activating FGFR3 mutations and translocations. About half of the tumours are sensitive to neoadjuvant chemotherapy. Therapies include GC/dose-dense MVAC, and possibly FGFR inhibitors.
- p53-like: infiltrated with stromal fibroblasts, bone metastases. Resistant to neoadjuvant chemotherapy. Therapies may include Met-inhibitors or initial surgery.
- Basal: enriched with squamous features, immature signature, angiogenesis. More common in women. Associated with advanced stage, metastatic disease at presentation, shorter DSS and OS in the absence of chemotherapy. About half of the tumours are sensitive to neoadjuvant

chemotherapy. Therapies include GC/dose-dense MVAC and possibly CTLA4/PD1/PDL-1, or VEGF inhibitors.
- Claudin-low/mesenchymal: clinical features are not well defined. Probably enriched with sarcomatoid features and associated with high metastatic potential.

6.8. Conclusions

An increasing number of studies are bridging the gap between translational science and novel biomarker-driven clinical trials, establishing molecular-based therapies for bladder cancer. For instance, expression analysis of DNA damage signalling proteins in tumour samples taken before irradiation could be used as a predictive marker of RT response and may ultimately allow patient selection for RT or cystectomy, thus improving overall cure rates.

Studies have demonstrated the feasibility of using whole-genome sequencing in the clinical setting to identify biomarkers of drug sensitivity that can aid in the identification of patients most likely to respond to targeted anti-cancer therapies.

Bladder cancer can no longer be thought of as a single disease; subtyping should be considered, and may have implications on selecting therapy. Application of biomarkers is set to fundamentally change bladder cancer treatment.

7. Perspectives for the future of UC
Joaquim Bellmunt, Spain

7.1. First-line therapies

As mentioned earlier, the advances achieved in the last 30 years of randomised trials evaluating systemic chemotherapy in the treatment of advanced bladder cancer are limited. Advanced bladder cancer seems to have reached a plateau with regard to median survival of patients, averaging approximately 15 months.

The standard chemotherapy regimens in 2015 for the first-line treatment or 'fit' patients are GC or MVAC or a regimen combining paclitaxel and GC in selected patients. GC and MVAC have level 1 evidence and grade A recommendation [21,135].

In 'unfit' patients, the combination of carboplatin and gemcitabine is now considered the best option based on a randomised phase II/III trial conducted in the EORTC (EORTC 30986) versus the previously used regimen M-CAVI [78].

Knowing that vinflunine is an effective drug with a safe profile in patients with impaired renal function, the open-label, multicentre, international JASINT-1 randomised phase II study assessed the combination of gemcitabine or carboplatin with vinflunine [87]. The initial promising data from JASINT-1 is being further evaluated in the JASINT-2 randomised phase III study comparing vinflunine–gemcitabine versus gemcitabine–carboplatin doublet combinations in 162 patients unfit for cisplatin with advanced or metastatic UC.

7.2. Second-line therapies

The most promising single-agent second-line chemotherapy is vinflunine, a third-generation semi-synthetic vinca

alkaloid. In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered; alternatively, due to the limitations in this setting, treatment within a clinical trial may be offered (grade A* recommendation) [21]. Currently, vinflunine is the only approved second-line drug and the only drug that has proven beneficial both within a phase III study and in real world data [98,101–103]. A long list of single-agent second-line chemotherapy trials is available for advanced bladder cancer (reviewed in [89]).

Vinflunine's mechanism of action is threefold, in that it is a microtubule inhibitor with anti-angiogenic activity that reverses epithelial-to-mesenchymal transition [136,137]. Moreover, it has anti-angiogenic activity at non-cytotoxic concentrations and can inhibit metastasis and impact on epithelial-to-mesenchymal transition at low doses (*in vitro* studies) [138–140].

7.3. Second-line targeted therapies

Many single-agent phase II studies with targeted therapies have been tested in the second-line setting, but no substantial activity has been demonstrated as single agents. These include gefitinib, bortezomib, lapatinib, sorafenib, sunitinib, aflibercept, pazopanib, volasertib, everolimus, vandetanib, temsirolimus, and dovitinib.

Furthermore, targeted agents combined with a cytotoxic drug (paclitaxel + cetuximab or docetaxel + vandetanib) in platinum-pretreated patients did not demonstrate additive activity and resulted in increased toxicities [94,95].

The VEGF pathway may play an important role in the pathogenesis of bladder cancer. Previous phase II trials failed to demonstrate activity as single agents, but more recent phase II combination studies have led to more promising results. Ramucirumab, a human VEGFR2-targeted monoclonal antibody, has demonstrated clinical activity in several solid tumours with preclinical testing supporting a role for ramucirumab/taxane combinations in UC. In an ongoing phase II study in the second-line setting of advanced or metastatic UC, patients were randomised equally to one of three open-label treatments: docetaxel (n = 44); docetaxel and ramucirumab (n = 46); or docetaxel and icrucumab (n = 49). Randomisation was stratified by the absence/presence of visceral metastases and receipt of prior anti-angiogenic therapies [96]. While docetaxel + icrucumab led to minimal activity (ORR 10%, disease control rate [DCR] 31%) and development of icrucumab was interrupted in bladder cancer, the ORR for docetaxel + ramucirumab was 19.6 versus 4.5% for docetaxel ($p = 0.0502$) and the DCR was 67.4 versus 43.2% ($p = 0.033$). Median interim PFS data were also significantly in favour of docetaxel + ramucirumab versus docetaxel: 22 weeks versus 10.4 weeks ($p < 0.001$), providing a basis for testing ramucirumab in a phase III study now enrolling 524 patients (docetaxel + ramucirumab versus docetaxel + placebo). Nevertheless, toxicities were increased in the docetaxel + ramucirumab arm with a high rate of FN (20% versus 11% with docetaxel only) (Table 15). The most common grade ≥III AEs from the interim analysis are summarised (Table 15) [96].

Another recent single-arm phase II study combined an angiogenesis inhibitor (pazopanib) with weekly paclitaxel in 32 pretreated patients with refractory urothelial cancer [97]. Objective responses were observed in 50% of patients, with PFS and OS values of 6 and 8 months, respectively. Seventy-five percent of patients required dose reduction and 44% of patients received growth factors. Despite the impressive ORR value, OS is similar to many other trials, and myelosuppression was significant. The initially planned phase III study was cancelled based on a corporate decision.

7.4. Maintenance therapy

Maintenance therapy has an established role in some diseases such as advanced non-small cell lung cancer, in which patients receive continuation maintenance therapy or switch to another agent (*e.g.* pemetrexed or erlotinib) based on the benefits observed in randomised trials [141–143]. The key objectives of maintenance therapy are to delay progressive disease and increase OS. Secondary objectives include the prevention of symptom deterioration and maintenance of PS to allow further therapy.

Which role and which UC patients would best benefit from such a treatment approach remains to be established. Maintenance therapy in UC was investigated with the receptor tyrosine kinase inhibitor sunitinib versus placebo after first-line chemotherapy in a randomised phase II, double-blind study. From 54 randomised patients, the median PFS was 2.9 months with sunitinib versus 2.7 months with placebo. Similarly, no difference in OS was reported (10.5 months with sunitinib versus 10.3 months with placebo). The study was limited by premature closure and a small sample size. Maintenance sunitinib was considered unlikely to confer benefit in this setting [144]. A second biomarker-driven trial with maintenance lapatinib in bladder cancer was presented at ASCO 2015. Despite selecting patients based on her1 and her2 status, the trial was unable to demonstrate any benefit [145].

Some additional ongoing trials are investigating the role of maintenance therapy in advanced UC after first-line chemotherapy. Phase II data in fit patients are expected from two trials. The JASIMA single arm trial is investigating vinflunine up to disease progression after first-line chemotherapy with up to four cycles of GC treatment. Responding patients with at least stable disease were included in the trial. The Spanish MAJA trial is a randomised multicentre study in which up to six cycles of primary treatment with GC were allowed. Fit patients with advanced or metastatic UC not progressing on palliative first-line cisplatin-based chemotherapy were randomised to receive vinflunine maintenance + BSC versus BSC alone. The first preliminary results from the MAJA study presented at ASCO 2015 (66 patients) indicated that maintenance vinflunine post-cisplatin has an acceptable tolerability profile in advanced UC patients. With a median follow-up of 7.2 months, the median PFS was increased by as much as 6 months (10.4 months in the vinflunine arm and 4.6 months in the BSC arm [$p = 0.058$]), suggesting that more mature data may lead to significant PFS differences between arms [146].

7.5. *Conclusions*

Molecular understanding of bladder cancer biology has lagged behind other solid cancers, which has represented a major barrier in improving clinical care. To date, vinflunine is the only therapy that has been established and has been approved by the European Medicines Agency for bladder cancer patients who recur or are refractory to platinum-based therapy. Data on vinflunine in first-line 'unfit' bladder cancer patients are highly promising and may be confirmed in the ongoing JASINT-2 phase III study. The role of maintenance vinflunine is under study.

Novel targeted therapies in adequately selected, genetically profiled patients might lead to improvement in therapeutic outcomes.

The new emerging immunotherapeutic approach using check-point inhibitors opens a bright future for a selected subgroup of advanced bladder cancer patients.

Conflict of interest statement

Joaquim Bellmunt has served on advisory boards of GSK, Novartis, Pfizer, Bristol-Myers Squibb, Merck and Genentech. Maria De Santis has received honoraria from, and served as a consultant for, Amgen, Astellas, Bayer, Celgene, Dendreon, Ferring, GSK, Janssen Cilag, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Aventis, Shionogi, Takeda and Teva/OncoGenex, and has received research grants from Pierre Fabre. Nicolas Mottet has received honoraria from, and served as a consultant for, Takeda pharmaceutical/Millennium, Jansen, Astellas, BMS, Bayer, IPSEN, Ferring, Novartis, Nuclétron, Pierre Fabre, Sanofi, AstraZeneca, and has received research grants from Takeda pharmaceutical/Millennium, Astellas, Pierre Fabre, Sanofi Pasteur.

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