comments

INTRODUCTION

Radical cystectomy, with a pelvic lymph-node dissection, is widely regarded as the 'reference standard' treatment for invasive bladder cancer [1]. Survival after cystectomy is predicted by the pathological stage of the primary bladder tumour and nodes, as well as the quality of cystectomy [2]. Chemotherapy may improve the subsequent survival [3], but even with combined therapy the quality of surgery influences the outcome. For example, a subset analysis of a randomized, cooperative group trial of neoadjuvant chemotherapy plus cystectomy showed that the surgical factors of margin status, extent of node dissection, number of nodes resected and individual surgeon's experience (by training and volume) were independent predictors of overall survival [4]. Neoadjuvant chemotherapy was more likely to improve the survival of patients with muscle-invasive bladder cancer if they received a high-quality operation by an experienced surgeon. Despite mounting evidence that the quality of surgery matters, there are no universally accepted standards for radical cystectomy and pelvic node dissection, because the quality of surgery varies widely among individual surgeons and patients

What constitutes an adequate radical cystectomy and pelvic node dissection for bladder cancer? What benchmarks can be used to define the quality of surgery in an individual patient? We attempted to derive a set of standards for radical cystectomy and node dissection by compiling the inclusive cystectomy experience of 16 surgeons operating on 1091 cases over 3 years (2000–2002) from four centres experienced in treating bladder cancer [5]. Participating surgeons performed cystectomy for cure or palliation in 'all comers', regardless of age or comorbidity, and declined to operate in <1% of patients for health reasons. Our collaborative surgical results reflect, as much as possible, what cystectomy can achieve in unselected patients presenting with diverse clinical situations.

STANDARDIZATION OF RADICAL CYSTECTOMY: TIME TO COUNT AND BE COUNTED

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We evaluated surgical and pathological features defined by radical cystectomy and pelvic node dissection among patients of varying ages, health states, clinical stages of bladder cancer, and previous treatments (pelvic surgery, chemotherapy and radiation therapy) for bladder or other pelvic malignant or benign disease. A quarter of the patients were aged >75 years and 20% were octogenarians; 16% had been treated previously. Half had advanced pelvic disease (pT3–4) and 20% had positive lymph nodes. Surgical endpoints included soft-tissue margin status, extent of pelvic node dissection, number of nodes examined and individual surgeon volume.

Of the 16 surgeons, seven operated on <50 cases, five on 50–100 and four completed >100. There was no significant difference between surgeons or institutions in the surgical quality or type of patient operated, except the surgeons with the highest volume tended to operate on more elderly, sicker, and pre-treated patients than surgeons with lower volumes. Surgeons used a standard or extended bilateral node dissection in 80% of patients and 20% had a limited (9%) or no node dissection (11%). A limited node dissection was used in 35% of patients aged >75 years and in half receiving previous extensive pelvic treatment. A standard node dissection was sometimes impractical if the operation had to be completed quickly in infirm patients, or was impossible because of previous pelvic surgery, chemotherapy or radiation.

Table 1 shows the surgical outcomes of margin status, extent of node dissection and average node counts, accounting for patient variability. Although the overall positive margin rate was 6.5%, margins were positive in 12% of patients with locally advanced disease. Older, and pre-treated, patients had less extensive node dissections and lower node counts than younger, healthier patients who had not received previous pelvic therapy. The mean (median) number of nodes examined for all patients was 12.5 (11), but varied widely among individual patients having anatomically similar node dissections. This variability could be from anatomical differences between individuals or could reflect differences in the method of pathological review. Using such benchmarks, we think that experienced surgeons who regularly perform cystectomy (at least 10 per year) should achieve negative surgical margins in >90% of cases and remove a mean of 10–14 nodes, recognizing that such standards will not be met in some of the most difficult cases.

Last, the issue of standards raises two questions. First, with so many variables to be counted, can acceptable and clinically useful standards for cystectomy be established at all? We think that general guidelines can be proposed, based on robust data combined from many institutions and surgeons performing cystectomy in largely unselected patients, rather than the experience of one surgeon. Surgeons are accountable for surgical margins, extent of node dissection and nodes because they are proxy measures of surgical quality correlating with bladder cancer outcome.

TABLE 1 *Standards of radical cystectomy and pelvic node dissection, using data from the Bladder Cancer Collaborative Group for 1091 patients aged <75 or >75 years with or with no previous treatment*

Variable	<75		>75	
	No	Yes	No	Yes
No. of patients	709	104	213	65
Positive margins, %	6	9.5	5.5	3
Standard/extended node dissection, %	90	65	76	40
Mean nodes	14	8	10	6

Second, are surgical standards important? We think they are for the outcome in individual patients, and for the design and evaluation of multimodal studies in bladder cancer. Who, where and how well surgery is performed could influence follow-up care, including adjuvant therapies. Recognized and accepted standards might also serve to elevate the overall quality of cystectomy in the future. This alone may prove to be as or more important than anticipated improvements in chemotherapy.

The practical issues involved in creating uniform standards for cystectomy can be formidable but are clearly surmountable. It is time for surgeons to count, and be counted.

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SHOULD THE THERAPEUTIC APPROACH TO PROSTATE CANCER WITH SEMINAL VESICLE INVASION BE REVIEWED: IMPROVING FUNCTIONAL RESULTS WITHOUT DIMINISHING ONCOLOGICAL OUTCOME?

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It is generally accepted that the presence of seminal vesicle invasion (SVI) in a resected specimen is an unfavourable prognostic factor in prostate cancer [1–3]. SVI has been reported in 5–13.6% of recent radical prostatectomy specimens [4–6]. Various studies have assessed the prediction of recurrence and prognosis in patients with prostate cancer and SVI treated by radical prostatectomy. In these studies, factors influencing prognosis have been identified by retrospective analysis, and include preoperative PSA level, age, Gleason score (biopsy and resected specimen) and percentage of cancer in biopsy specimens [7–11].

In refining these criteria, Ramsden and Chodak [12] described a significant improvement in prognosis for men with SVI if the histology showed negative margins, unilateral SVI or perineural invasion. They concluded that this may be applied to patients with SVI to direct adjuvant therapy and guide postoperative counselling.

At the other end of the prognostic spectrum, what should the surgical approach be with regard to the SVs? It has been suggested that predicting SVI before surgery would enable surgeons to develop a SV-sparing prostatectomy, in the belief that this may reduce morbidity. It has been argued that preserving the SVs may result in less dissection close to the neurovascular bundle, with a theoretically lower risk of damaging it. It still has to be determined whether extirpation of the SVs changes the outcome. Some argue that SVI is the harbinger of metastatic disease, and therefore that any radical local treatment is destined to fail if SVI is present.

There are several counter-arguments; after the prostate has been removed the SVs serve no known purpose, and that the higher risk to the neurovascular bundle might be from dissection around the prostatic apex, rather than during SV dissection. In addition, there is a risk of leaving undetected carcinoma from isolated metastasis to the SV tip, even if the cut margins of the amputated SV are free from tumour. Type 3 SVI (isolated metastasis) is found in 13% of specimens containing SVI [13].

The current approach by some British surgeons is partial amputation of the SVs, as opposed to complete excision. This permits some pathological assessment of SVI, allowing an evaluation of the prognosis. Traditionally, unlike lymph node sampling, it was thought that resecting the SVs was of therapeutic rather than diagnostic value. It is likely that tumour metastasis to the tip of the SV would be missed by this technique. However, it is unlikely that SV dissection would be therapeutic if SVI is present.

Unfortunately SVI is still difficult to predict before surgery by imaging, a DRE or SV biopsy in patients with localized prostate cancer [14–18]. A trial involving patients with similar preoperative potency, randomized to partial or complete excision of the SVs, might be of interest. However, until clinicians are able to

confidently predict patients at low risk of SVI before surgery with a guarantee of oncological safety, the current practice of extirpation of the seminal vesicles at radical prostatectomy should continue.

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ADJUVANT TOPICAL TREATMENT OF UPPER URINARY TRACT UROTHELIAL TUMOURS – JOHN P. O'DONOGHUE and JEREMY P. CREW –

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INTRODUCTION

TCC of the ureter and renal pelvis is relatively uncommon and accounts for <5% of all cases of urothelial neoplasia. The standard treatment has been nephroureterectomy with excision of a cuff of bladder. The idea of organ-sparing surgery was first reported in 1945 for ureteric tumours [1]. With developments in endoscopic and percutaneous techniques, organ-sparing surgery is feasible in patients with inadequate renal reserve, at high risk of bilateral disease, or with significant comorbidity. Organ-sparing surgery is also suited to patients with low-grade disease and a normal contralateral kidney, because these lesions have a low risk of invasiveness and metastasis. Huben *et al.* [2] reported a median survival of 66.8 months for patients with low-grade vs 14.1 months for those with high-grade disease. In 83% of these patients, low- and high-grade tumours matched low- and high-stage disease. Percutaneous treatment is possible when the ureteroscopic approach is difficult. Inaccessible infundibulo-calyceal tumours or large pelvic tumours are more readily treated by the percutaneous approach. This route may be necessary in patients where retrograde access is difficult because there are anatomical anomalies.

With more conservative treatment it was reported that the ipsilateral recurrence rate is high (a third) but there were few patients in the study (14) and the follow-up was 2–11 years [3]. To minimize the risk of recurrence and because of the success of intravesical agents in the treatment of superficial TCC of the bladder, several reports have investigated their role in adjuvant treatment after organ-sparing surgery of the upper tracts. BCG therapy has been most commonly used but other agents, including mitomycin C, thiotepa,

adriamycin and interferon-α have also been tried. The agent can be instilled directly through a nephrostomy tube after the position has been checked by imaging, to prevent obstruction or extravasation. The agent is instilled via gravity and linked to a manometer so that the intrarenal pressure does not exceed 25 cmH$_2$O [4]. Alternatively, it may be given retrogradely via a ureteric catheter, by bladder instillation with the patient in the Trendelenberg position after inserting a ureteric stent, or via a urethral catheter in a patient with VUR [5].

Unfortunately, the results of intravesical treatment are varied. Herr [6] reported on a patient with a single kidney and a pT2G3 papillary tumour and multifocal carcinoma *in situ* at the PUJ. After pelvectomy, ureterectomy and autotransplantation the patient received six weekly courses of intravesical BCG. Thirteen months after surgery the patient was free of recurrence and had negative cytology. A report by Orihuela and Smith [7] found an 80% recurrence rate in patients who did not receive adjuvant BCG, vs 17% among those who did. However, a follow-up study showed no survival advantage with adjuvant immunotherapy [8]. Studer *et al.* [9] used Pasteur BCG in 10 renal units (eight patients) with cytological evidence of carcinoma *in situ*. In all but one patient the cytology became negative. A study by Martinez-Pineiro *et al.* [10] of 42 upper tracts treated solely by endourological means gave a recurrence rate of 24%. After intravesical adjuvant BCG or mitomycin C the recurrence rate was 12.5% and 14%, respectively (mean follow-up 30.6 months). Shoenberg *et al.* [11] reported on 10 patients with solitary kidneys and upper tract TCC; the patients received an intravesical BCG instillation as an adjunct to percutaneous resection, with no reported morbidity. Six of the patients had no recurrence, one had recurrence at 19 months, and one developed metastases at 15 months. One died from disease progression. Further studies using topical BCG after organ-sparing surgery are listed in Table 1 [12–16].

Mitomycin C is a cross-linking agent and in part inhibits DNA synthesis. Topical mitomycin C is well tolerated in the upper urinary tract and there are no reports of impairment in renal function after instillation. Smith *et al.* [17] reported on two patients with bladder cancer and VUR who developed lower ureteric recurrences. They received

intravesical treatment for 18 months, and after 2 years they were reported to be disease-free. Eastham and Huffman [4] reported on the use of mitomycin C as topical therapy after endoscopic resection of superficial TCC of the renal pelvis or ureter. Seven patients were treated over a 4-year period and were either not fit for more aggressive treatment or had a solitary kidney. Five patients had no evidence of disease whilst one had a marked decrease in tumour burden. Table 1 also shows other studies using mitomycin C [4,18].

After radical cystectomy, 2.4–8.5% of patients develop upper tract TCC [19]. Factors associated with a greater risk of recurrence after surgery include high grade and stage, multifocality, carcinoma *in situ*, and TCC in the prostatic urethra and distal ureter [20]. Recurrence in the upper tract after cystectomy is usually aggressive and has a poor prognosis. The treatment of choice is nephroureterectomy but in patients with bilateral disease or a solitary kidney, and low-grade/low-stage disease, conservative treatment has been used; whilst the results appear encouraging, the follow-up is short and patients few [21].

Upper urinary tract tumours are rare and the most appropriate treatment for low-grade tumours is not entirely clear. The results appear encouraging but no individual study has shown a statistical improvement in survival and recurrence rates. What is known about intravesical chemotherapeutic and immunological treatments after conservative surgery is from retrospective studies with small cohorts of patients and with heterogeneous characteristics. The reasons

for inconclusive results include; (i) too few patients to show clinical significance; (ii) inadequate contact time between the urothelium and the agent being instilled; and (iii) possible differences between upper tract tumours and bladder tumours. Large prospective multicentre studies are needed to clarify the situation. Meanwhile, ablative surgery remains the standard for managing upper tract TCC but in circumstances where this may be problematic, conservative resection with adjuvant topical chemotherapy/immunotherapy is an option.

TABLE 1 *Studies using adjuvant topical BCG or adjuvant mitomycin C after organ-sparing surgery*

Ref	N patients	Regimen	Tumour stage/grade	Recurrence rate (%)	Follow-up, months
BCG					
[12]	17	Retrograde	Ta/T1/CIS/G2–G4	28.5	11–64
[13]	14	Percutaneous	NG	12.5	NG
[14]	13	Percutaneous	Ta/G1–G2	13	6–36
[15]	8	Percutaneous	NG	12.5	9–59
[16]	9	Retrograde	NG	22	4–41
Mitomycin C					
[4]	7	Percutaneous	NG	28.5	1–12
[18]	20	Retrograde	G1–G3	54	30

NG, not given.

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RED–CELL SALVAGE IN UROLOGICAL SURGERY

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Significant blood loss during major urological surgery is common and in the UK is usually replaced by transfusion of donated homologous blood. This is not always entirely satisfactory because of the increasingly limited availability and the well-documented risks associated with homologous blood transfusion. Most recently concerns have been raised about possible contamination of donated blood with variant Creuzfeldt-Jakob disease [1] which has caused the Blood Transfusion Service to discontinue donations from those who have received a blood transfusion since 1 January 1980. This is likely to have a significant affect on the stocks of donated blood and means that alternatives to homologous blood transfusion should be actively pursued.

Autologous blood transfusion is the collection of blood from an individual for the purpose of re-infusion into the same individual at a later time. Autologous blood transfusion can be in the form of preoperative autologous blood donation (PABD), intraoperative cell salvage (IOCS) or postoperative cell salvage and acute normovolaemic haemodilution (ANH).

The first PABD was described in 1921 by F.C. Grant in a patient undergoing surgery for a cerebellar tumour. PABD became standard medical practice in the 1920s and 30s and was frequently used by Cushing during cranial surgery. It was not until World War II that transfusion practice changed and homologous products became readily available.

Cell salvage with direct reinfusion was described in haemothorax cases in 1931 by Brown and Debenheim. In 1943 Arnold Griswold developed the first cell salvage auto-transfusion device, collecting blood in a bottle by suction, straining it through a cheese cloth and then re-infusing it. Modern cell salvage techniques still use this basic principle.

In ANH, 1–3 units of whole blood are drawn from the patient after the onset of anaesthesia and the volume is replaced with colloid or crystalloid volume expanders. Any blood lost during surgery is therefore more dilute and the withdrawn blood can be re-infused at the end of the procedure.

In modern cell salvage techniques (IOCS) salvaged blood is aspirated from the surgical field, anticoagulated in the suction device and then collected in a sterile collection container. When an adequate amount of blood has been collected it is pumped into a spinning centrifuge bowl. Red cells, being the heaviest components of blood, collect at the lowest point in the bowl and supernatant containing the other components of blood spill over into a waste bag. Sterile saline solution is pumped through the spinning centrifuge bowl and displaces the lighter remaining contaminants. Once this process is complete the red blood cells are re-suspended and can be transfused, usually immediately, or can be stored under specific conditions for up to 6 h.

IOCS has become the mainstay of many general surgical operations where there is a large volume blood loss, e.g. ruptured aortic aneurysm repair, greatly reducing the need for homologous blood transfusion. However, there has been concern that IOCS is not safe in the presence of malignant disease, because malignant cells may spill into the operative

field, be taken into the cell salvage machine, and because they are heavy like red cells, returned to the patient. The use of leukocyte depletion filters can reduce the risk of such occurrence but concerns remain as to whether use of IOCS may compromise surgical cure. Malignant cells have been found in the circulation during surgery even when IOCS is not used [2], but the significance of these circulating cells is not clear. If re-infused cells were clinically significant it would be expected that patients having had IOCS might present with early widespread metastases, or at least unexpected lung metastases. This has not proven to be the case in bladder, renal or prostate cancer. The four reports in Table 1 [3–6] illustrate experience of nearly 250 cases of IOCS, with no cases of early unexpected metastasis.

Since 1996 it has been the policy in our unit to have IOCS available at all major open urological surgery. We have experience of >150 cases, including 74 cystectomies, 30 radical nephrectomies and 37 radical prostatectomies, and have transfused over 600 units of salvaged blood. There have been no cases of early lung or diffuse metastases suggestive of spread of malignant disease by IOCS.

The theoretical risk of metastatic spread secondary to IOCS has not become apparent, although the very real risk of spread of viral infection and other complications of homologous transfusion remain.

TABLE 1 Reports of IOCS in urology

Ref	Date	N patients	Operation	Outcome	Comment
[3]	1986	24	RC	Two died from local recurrence, LN met	IOCS is safe
		10	RP	One pelvic recurrence	
		13	RN	Two lung metastases	
[4]	1989	49	RC	Six patients died by follow-up mean 23.8 months	Overlap of patients with above series
[5]	2003	87	RP	No difference in outcome for IOCS over pre-donation or no transfusion	IOCS is safe
[6]	2001	62	RP	No difference in progression-free survival with 101 patients who pre-donated blood	No increased risk of early biochemical progression

RC, RP, RN, radical cystectomy, prostatectomy, nephrectomy.

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