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Renovascular hypertension: diagnosis and management

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INTRODUCTION

Renovascular hypertension (RVH) results from stenosis of the main renal artery or one of its major branches. The true prevalence of RVH is unknown but it may account for 1–5% of all cases in adults and is more likely to be a factor in those with resistant or malignant-phase hypertension [1]. Renal artery stenosis (RAS) may be caused by a heterogeneous group of conditions, but >90% of cases are accounted for by atherosclerotic renovascular disease (ARVD) or fibromuscular dysplasia (FMD) of the renal artery. Kawasaki’s or Takayasu’s arteritis are relatively more common in some ethnic groups, and rare causes of RVH include thrombosis, embolism and dissection of the renal artery, RAS associated with extrinsic compression and pheochromocytoma, and aortic coarctation. Although most hypertension is essential, the possibility of RVH should always be considered, particularly in groups at increased risk, because first, it is potentially curable, and second, progressive disease can lead to ischaemic injury and renal failure.

CAUSES OF RVH

ARVD

RVH is most commonly caused by ARVD, although most patients do not have a significant atherosclerotic RAS (ARAS). Most patients present with a long history of hypertension in the context of systemic atherosclerosis, which is exacerbated by obliteration of the distal renal vasculature, leading to renal ischaemia, renal failure and hypertension. The diagnosis of ARVD should always be considered if there is evidence of atherosclerosis affecting peripheral, cerebral or coronary arteries. Other risk factors include age, male gender, smoking and a history of hypertension, diabetes mellitus or hyperlipidaemia. The true prevalence of ARVD is unknown but there are data on the prevalence of ARAS. Early data from autopsy studies reported an age-related increase in incidence of severe ARAS from 5% in those aged <64 years to 42% in those aged >75 years [2]. Other data comes from studies in which renal artery imaging was undertaken in patients being investigated for arterial disease elsewhere. ARAS of >50% has been reported in 35% of elderly patients with heart and renal failure, 20–35% with aorto-iliac disease, 15–40% with peripheral vascular disease and 5–20% with coronary artery disease [3]. However, the significance of these data are questionable, given the difficulty in being certain whether a stenosis is functionally significant and problems with interobserver agreement, even with ‘gold standard’ of angiography. However, from experimental and clinical studies, an arterial stenosis of 60% is a useful threshold at which the likelihood of progression of disease and occlusion of the artery is significant [4], although a stenosis of >80% may be required to cause RVH. A recent population-based study has estimated the prevalence of ARAS which exceeds 60% as 6% in those aged >65 years [5].

The clinical presentation of ARVD is protean. Although hypertension is not always the presenting complaint [6], the diagnosis should be considered in patients with resistant hypertension, hypertension that has recently escaped control or those presenting with an acute coronary or cerebrovascular event in the context of uncontrolled hypertension. Other patients present with progressive renal insufficiency, proteinuria, nephrotic syndrome [7,8], or the incidental finding of renal asymmetry. The diagnosis may be suggested by a rise in creatinine level (or rarely, acute renal failure) after introducing an angiotensin II inhibitor (either and angiotensin-converting enzyme, ACE, inhibitor or angiotensin II receptor blocker) which are prescribed with increasing frequency. Congestive cardiac failure or episodes of acute ‘flash’ pulmonary oedema which occur in the absence of an acute coronary event can be the presenting complaint [9,10]. Clinical signs include a wide arterial pulse pressure, which reflects loss of arterial compliance, bruits over the renal and other major arteries, absent or weak popliteal and pedal pulses, and a reduced ankle-brachial pressure index.

ARAS is bilateral in about half of all cases and is a progressive disease. Retrospective analysis of several studies which used serial angiography estimated that progression occurs in up to 49% of vessels, with total occlusion occurring in 14%. These studies probably overestimate the rate of progression, as the decision to carry out angiography is likely to have been influenced by clinical deterioration. A prospective study using serial renal Doppler ultrasonography estimated the rate of progression at 3 years to be 35%, with an annual occlusion rate of 3.1%. Renal atrophy may also be a marker of progression and is present in 20% of kidneys with a stenosis of >60% [11]. However, in 85 patients with ARAS who had repeated angiography, Schrire et al. [12] reported progression of stenosis in 44% of kidneys, whereas renal atrophy (defined as reduction in renal length of >1.5 cm) affected 70%. A recent prospective study using serial Doppler ultrasonography showed that the 2-year cumulative incidence of renal atrophy (>1 cm) was 5.5%, 11.7% and 20.8% in kidneys with no stenosis, <60% stenosis and >60% stenosis, respectively. These studies confirm the idea that when considering the natural history of ARAS it is important to evaluate progression not only in the degree of luminal narrowing, but also the extent of renal parenchymal damage. In ARAS it is apparent that both kidneys are at risk of parenchymal damage whether the stenosis is unilateral or bilateral. This principle is well illustrated by Doppler findings of bilateral abnormal renal haemodynamics in patients with unilateral ARAS [13] or in a study in which electron beam CT showed a reduction in renal cortical blood flow in ARAS compared to FMD [14]. Further support is provided by measurements of individual kidney function in patients with confirmed ARAS, which show a significant correlation between the degree of stenosis and isotopic GFR. However, that study also showed that in patients with unilateral stenosis there was no difference in GFR between the stenosed and the unstenosed kidneys [15]. These findings emphasize that ischaemia from proximal stenosis is not the only cause of parenchymal injury in ARAS.

FMD

This accounts for ~10% of cases of RVD; it is commoner among women usually aged...
15–50 years, although any age may be affected and it has been reported from infancy to old age. In most (85%) cases there is medial fibroplasia characterized by an aneurysmal and beaded appearance at angiography (Fig. 1). Other cases are due to peri-arterial fibroplasia or intimal fibroplasia and can be associated with arterial dissection. The mid to distal part of renal artery is most commonly affected but intrarenal segmental branches can be involved. Other than an association with cigarette smoking [16], the pathogenesis remains obscure but mural ischaemia due to functional defects in the vasa vasorum, possibly in association with developmental renal malposition, has been postulated. Other conduit arteries can be abnormal and FMD should be excluded in young people presenting with acute carotid artery dissection or occlusion. The diagnosis should be excluded in any young person presenting with severe hypertension, particularly in the presence of an abdominal bruit and in the absence of a nocturnal decrease in the 24-h blood pressure record, which is suggestive of secondary hypertension [17].

The natural history of FMD is variable and not necessarily benign [18]. Although Pohl and Novak [19] reported disease progression in 33% of 66 patients with FMD, no stenosis progressed to complete occlusion and there was no clear association with renal atrophy. However, Goncharenko et al. [20] reported on 42 patients (half of them male) with angiographic evidence of progressive disease over 4–136 months of follow-up. In their study, 25% of affected arteries developed total occlusion and 62% of affected kidneys atrophied (>0.5 cm reduction in renal length). In contrast to ARVD (Fig. 2), the renal microcirculation is normal and therefore progressive renal atrophy is due to haemodynamically significant proximal arterial stenosis which needs to exceed 75–80%. A recent spiral CT study showed cortical thinning in unilateral fibromuscular renal artery stenosis, and cortical imaging is probably important to identify haemodynamically significant stenoses [21].

The presenting features of ARVD and FMD are:

ARVD
- Hypertension.
- Rise in creatinine level after introducing and ACE inhibitor or angiotensin II receptor blocker.
- Proteinuria.
- ‘Flash’ pulmonary oedema

FMD
- Early onset of severe hypertension with loss of physiological diurnal blood pressure variation.
- Deterioration of renal function.

TAKAYASU’S ARTERITIS AND GIANT CELL ARTERITIS

Takayasu’s arteritis affects the aorta and its distal major branches. It is typically a disease of young women in their second to fourth decades, and which is much commoner in Asia than in Europe. In contrast, giant cell arteritis tends to involve carotid artery branches of Northern Europeans aged > 50 years. Both conditions feature acute inflammation and subsequent fibrosis, which leads to stenoses including aortic coarctation, aneurysmal dilatation and distal ischaemia. Both conditions can cause RAS, RVH and ischaemic renal injury, but this is more common with Takayasu’s arteritis [22]. Initial therapy is steroid immunosuppression, possibly supplemented with cytotoxic therapy. Severe RVH which cannot be controlled medically may respond to angioplasty or bypass surgery.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid antibodies, either isolated (i.e. primary antiphospholipid syndrome) or occurring in the context of an autoimmune disease such as systemic lupus erythematosus, are associated with both arterial and venous thromboses. The histology is not specific and may reflect a focal inflammatory process or an underlying predisposition to premature atherosclerosis, possibly due to a cross-reaction between antiphospholipid antibodies and oxidized low-density lipoproteins. RAS has been reported in patients with both primary and secondary disease [23,24]. Medical management includes treating the underlying disease and anticoagulation with aspirin and/or warfarin.

TRANSPLANT RAS

RAS can complicate renal transplantation, although the incidence is unknown [25]. The stenosis is usually anastomotic, with a lower incidence when an end-to-side anastomosis is formed between the donor aortic patch surrounding the renal artery origin and the recipient’s external iliac artery. The pathogenesis may involve atherosclerosis, a peri-arterial fibrous stricture, chronic rejection or kinking of the vessels, which leads to a functional stenosis. Clinical features include worsening or refractory hypertension, insidious graft dysfunction, fluid overload and even pulmonary oedema.

PATHOGENESIS OF HYPERTENSION IN RAS

The pathophysiology of hypertension in RAS was first described by Goldblatt [26]. In unilateral disease, arterial perfusion pressure...
in the stenosed kidney is reduced, which leads to activation of the renin-angiotensin-aldosterone (RAA) system. Angiotensin II-dependent hypertension results in a pressure natriuresis through the contralateral kidney. In bilateral stenoses, there is RAA activation with volume expansion and hypertension which ultimately leads to feedback inhibition of the RAA system. In both experimental models, systemic RAA activation is not sustained and increased endothelin production, local RAA activation, arterial wall remodelling and oxidative stress are responsible for maintaining the hypertension. These local paracrine and structural changes may also contribute directly to renal injury, in addition to the effects of the hypertension itself, and therapeutic strategies have been tested with some success [27–29].

Clinically, the situation is more complicated, particularly with ARAS, which is usually bilateral and frequently complicated by coexistent renal failure. Renal parenchymal damage results not only from ischaemia due to proximal RAS but also from small vessel atherosclerosis and atheroembolism of platelet and cholesterol thrombi derived from unstable atherosclerotic plaques [30].

INVESTIGATION OF RAS

An ideal investigation for RAS would be noninvasive, accurately quantify the stenosis, provide functional information and identify those stenoses that are likely to benefit from intervention. Ultrasonography can be used to measure renal size and detects renal asymmetry that may be due to RAS. Importantly, kidneys <8 cm long are unlikely to benefit from revascularization procedures. Duplex Doppler ultrasonography can be used to identify RAS of >50% but this test is operator-dependent and may still be unsuccessful in 20% of patients. The haemodynamic consequences of the stenosis can be quantified by calculating the resistive index, as 1 = (end diastolic velocity/maximal systolic velocity). In a recent prospective study, a resistive index of >0.8 predicted a poor response to angioplasty [31].

Captopril renography is a functional test used to detect the angiotensin II dependence of GFR; in a positive test, the pre-administration of oral captopril 25–50 mg delays the uptake of tracer, reduces peak uptake, prolongs parenchymal transit and slows excretion, as well as affecting divided function in unilateral disease [32]. The utility of the test may be limited by confounding factors, e.g. volume depletion, concurrent medication and underlying renal dysfunction, so careful preparation of the patient is mandatory. It is widely used as a screening test for RAS and to assess the safety of angiotensin II inhibitors, but in reality provides little additional information than an assessment of plasma creatinine level 3–5 days after introducing the drug. However, its most useful role is probably in predicting the benefit from revascularization of a stenosed kidneys [33]. Most data are from studies of patients with RAS due to FMD and there are few available data from patients with ARAS or advanced renal dysfunction.

CT angiography (CTA) and MR angiography (MRA) are becoming the accepted standard for noninvasive imaging of renal arteries. A meta-analysis showed the superiority of both these techniques over both captopril renography and ultrasonography [34]. CTA is as accurate as MRA but has the disadvantage of radiation dose and radio-contrast volume. Although contrast-enhanced (gadolinium) MRA is highly accurate for assessing RAS, with 97% sensitivity and 93% specificity, most data come from specialist centres and there may be significant publication bias. A negative contrast-enhanced MRA probably excludes significant stenosis but false-positives due to turbulence are more likely. Currently, MRA is used as a second-line test after a positive screening test or after a negative screening test (5–10% false-negatives) when the index of clinical suspicion is high. As availability increases it is likely that MRA will become the screening test [35].

Contrast arteriography with aortography and selective renal artery cannulation remains the ‘gold standard’ in assessing renal artery anatomy. It is particularly useful in the early detection of FMD, the diagnosis of intrarenal branch artery stenoses and in kidneys with complex anatomy, including multiple accessory arteries. Disadvantages of this technique include significant interobserver variation in assessing the degree of stenosis, the absence of functional information, and the risks of contrast nephropathy and cholesterol emboli syndrome. Contrast arteriography is used routinely before angioplasty or surgical intervention but its role as a diagnostic test is being re-defined with the increased availability of MRA.

MANAGEMENT OF RAS

FMD

In patients with FMD, the RAS tends to be post-ostial and highly amenable to percutaneous transluminal angioplasty. Although this method may completely relieve the stenosis and cure hypertension in FMD, most patients still require some antihypertensive medication, and up to 25% will have re-stenosed after a year [36]. Stenting is unattractive, given the relative youth of these patients, and surgical intervention may be more appropriate with complex stenoses. Optimum medical management of hypertension is essential to minimize life-time cardiovascular risk.

ARAS/ARVD

There is still considerable controversy about the optimum management of ARAS. Most of these patients have hypertension, diabetes and disseminated atherosclerosis, with a more than five times greater risk of cardiovascular death than age-matched controls [37]. Thus the assessment of benefit of an intervention must include not only preserving renal function and improving control of hypertension, but also reducing overall cardiovascular risk.

MEDICAL MANAGEMENT

All patients should receive lifestyle advice on weight reduction, stopping smoking and reducing dietary salt intake. Anti-platelet agents such as aspirin have confirmed benefit in reducing morbidity and mortality in cardiovascular disease. Dyslipidaemia is usually present in patients with ARVD although the severity does not predict the progression of ARAS [38]. There are no published studies which specifically report the use of statins in ARAS, although their benefit in improving cardiovascular outcome in high-risk patients is well established [39]. In addition to lowering lipids, statins are anti-inflammatory and stabilize atherosclerotic plaques [40,41].

The great majority of patients will have hypertension which usually requires multidrug regimens, including β-blockers,
calcium antagonists, diuretics and α-blockers. Angiotensin II inhibitors are particularly useful in patients with diabetic nephropathy, left ventricular hypertrophy and heart failure but may reduce renal function in patients with unilateral or bilateral RAS. In a prospective study which examined the safety of ACE inhibitors in ARAS, 69 of 108 patients had a 20% rise in plasma creatinine levels, and of these, 52 had severe disease (bilateral disease or stenosis of a single kidney). Importantly, no patient developed oliguric renal failure and creatinine levels returned to baseline after stopping the drug. These data suggest that angiotensin II inhibitors can be used safely in patients at risk of ARAS. However, these drugs should be started at a low dose and renal function tested after 3–5 days, and then again after subsequent dose increments. Concurrent diuretic therapy should be avoided initially. The drug should be stopped if there is a significant increase in creatinine level and the patient should be considered for revascularization.

REvascularization

Whilst the value of optimizing medical therapy to reduce cardiovascular morbidity is undisputed, its role in delaying the progression of nephropathy is less clear, as there are few published data on patients assigned to medical therapy alone. In a series of patients selected for medical therapy, 10% required urgent revascularization for uncontrolled hypertension or progressive renal impairment, and the overall mortality was 28% after a mean follow-up of 38 months. Three recent randomized controlled studies compared medical therapy with and without angioplasty, and showed no difference in either blood pressure control or preservation of renal function. However, in the largest of these studies, half of patients assigned to medical therapy alone crossed over to receive angioplasty for poorly controlled blood pressure within 3 months. Finally, the reported incidence of major complications from angioplasty with or without stenting is considerable, at 11–13% [47].

The true role of revascularization surgery is uncertain, not least because of there are no properly conducted studies which involve a cohort randomized to the best medical management. Surgical procedures range from endarterectomy to arterial bypass and their evaluation is beyond the scope of this brief review. Available outcome data emphasize the importance of case selection, focusing on the patient’s age and systemic burden of atherosclerosis. Non-randomized retrospective studies have shown the effectiveness of surgical revascularization, but a prospective study which compared percutaneous transluminal renal angioplasty with surgery in ostial stenosis showed no benefit for surgery. Currently, surgery should be reserved for those in whom medical and radiological intervention have failed.

Conclusion

RAS should be excluded in young patients presenting with hypertension and in older patients with resistant hypertension, acute renal dysfunction induced by angiotensin inhibitors, or unexplained episodes of ‘flash’ pulmonary oedema. In FMD, positive captopril renography supports intervention, although hypertension is unlikely to be cured. In ARAS, the indications for and benefits from intervention are less clear. Our current practice is to attempt angioplasty and stenting in patients with bilateral disease in whom the contralateral kidney is virtually without function, in patients with recurrent ‘flash’ pulmonary oedema, and in those who have a rapid decline in renal function after introducing an angiotensin II inhibitor and in whom there is a strong indication for that treatment.

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Abbreviations: RVH, renovascular hypertension; (A)RAS, (atherosclerotic) renal artery stenosis; ARVD, atherosclerotic renovascular disease; FMD, fibromuscular dysplasia; ACE, angiotensin-converting enzyme; RAA, renin-angiotensin-aldosterone; CTA, CT angiography; MRA, MR angiography.
Current aspects of the surgical management of organ-confined, metastatic, and recurrent renal cell cancer

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INTRODUCTION

RCC comprises 2–3% of human malignancies, but a review of patients recorded in the Connecticut Tumor Registry indicates a sixfold increase in prevalence of RCC from 1935 to 1989. In 2003, there were >31 000 new cases of RCC diagnosed in the USA [1], an incidence that has more than doubled since 1950. The introduction of new and subsequently refined imaging methods such as ultrasonography and CT into clinical routine has resulted in the early diagnosis of more patients with RCC at an early tumour stage. Although this development has improved patients’ clinical prognosis in general, even organ-confined tumours of comparable stage and grade can show a diverging biological behaviour. Currently, regardless of tumour stage, the average 5-year survival rate of RCC patients has improved to only 50% [2], possibly because, to date, there are no suitable adjuvant therapeutic options available for treating locally advanced or metastatic RCC.

THE MANAGEMENT OF ORGAN-CONFINED RCC

A perifascial nephrectomy that includes removing the tumour-bearing kidney, combined with adrenalectomy [3], is still considered the standard treatment for RCC. However, together with further refinements of imaging methods available for preoperative tumour staging, an improved understanding of the biology of this malignancy allows a better adjustment of the therapeutic approach to the individual clinical situation.

First, nephron-sparing surgery (NSS) has become a well established treatment for organ-confined RCC after it was shown that it does not increase the frequency of local tumour recurrences and does not adversely affect the patients’ life-expectancy when compared with radical nephrectomy (RN). However, the question about the maximum tumour diameter for which an organ-preserving strategy can still be safely recommended remains to be clarified [3].

Second, solitary adrenal metastases occur in 1–10% of patients with RCC [4]. Thus, routine adrenalectomy combined with RN is an overtreatment in most cases. Because most intradrenal lesions can be detected before surgery, and neither size nor location of the primary lesion within the tumour-bearing kidney appear to correlate with a greater risk for the presence of intra-adrenal metastatic spread, it is currently recommended to omit routine adrenalectomy during surgery for RCC [4].

Third, neoplastic involvement of the renal veins or the inferior vena cava, which occurs in 10–25% of patients, was shown to have no independent prognostic effect on clinical prognosis. Therefore, in the absence of regional lymph node or distant metastases, the surgical removal of an intracaval tumour thrombus can be considered a curative therapy [5].

Since its introduction, laparoscopic nephrectomy is being increasingly used in many institutions worldwide. Whether retroperitoneal or transperitoneal, the laparoscopic approach must duplicate established open surgical oncological principles, i.e. early control of the renal vessels before tumour manipulation, wide specimen mobilization external to Gerota’s fascia, avoidance of specimen trauma or rupture, and intact specimen extraction. In the hands of experienced laparoscopic urological surgeons, and with adherence to the above-mentioned principles of open RN, laparoscopic RN may now be considered a standard of care for patients with T1–3a N0M0 RCC, and intermediate outcome data indicate equivalent cancer-free survival to that from open radical nephrectomy in such cases [6]. However, the open approach remains the preferred technique for patients with any of the following characteristics: major venous or vena caval involvement, local tumour invasion, massive tumour, gross lymphadenopathy, and metastatic disease requiring metastasectomy.

The frequency of NSS is also increasing, although the long-term functional advantage when there is a normal opposite kidney remains to be confirmed. However, first data indicate that one of the main benefits of maximum nephron preservation includes the decreased risk of progression to chronic renal insufficiency and end-stage renal disease [7,8].

Standard indications for NSS can be categorised as absolute, relative and elective. Absolute indications include circumstances where the patient would be anephric after RN. These patients have either bilateral RCC, or a tumour involving a solitary kidney. Relative indications include patients with unilateral tumours, and a functioning opposite kidney, affected by a condition which might threaten its function in the future. Relative indications also include patients with hereditary forms of RCC, with a high likelihood of developing tumours in the future. Elective indications for NSS include patients with localized unilateral RCC and a normal contralateral kidney. Recent studies have clarified the role of NSS in such patients. Data from the Cleveland Clinic and Memorial Sloan-Kettering Cancer Center indicate that RN and NSS provide equally effective curative treatment for such patients who present with a single, small (<4 cm) and clearly localized RCC [9–11].

RADIOFREQUENCY (RF) ABLATION FOR RCC

Image-guided percutaneous RF ablation continues to gain attention as a treatment option for the focal destruction of solid tumours. Potential advantages of this technique include reduced morbidity,
outpatient therapy, and the ability to treat poor surgical candidates. Although historically the main indication for RF was the treatment of hepatic lesions, more recently the clinical potential of RF ablation has expanded, including the treatment of kidney tumours. Indications for RF ablation include small, incidentally found renal cortical lesions in elderly patients, imaged for other comorbid conditions, patients with a genetic predisposition to multiple tumours, or patients with a solitary kidney, or bilateral RCCs [12].

RF delivers a high-frequency (460–500 kHz) alternating current into the tumour using an RF electrode, a thin needle (21–14 G) that is electrically insulated along all but the distal 1–3 cm of the shaft. The application of RF current produces resistive friction in the tissue that is converted into heat, which in turn induces cellular destruction and protein denaturation at temperatures of >50°C when applied for 4–6 min, and almost instantaneous destruction at >60°C [13]. Electrodes can be placed directly into the tumour using ultrasonography, CT, or MRI guidance. The success of the procedure is usually assessed by imaging afterward, typically by CT at least a month after treatment. Imaging immediately after the procedure can be difficult to interpret because peripheral inflammation may mimic the appearance of viable tumour. On CT, viable tumour maintains its enhancement (>10 Hounsfield units after injection with contrast medium), whereas successfully ablated tumour loses its attenuation [14].

Contraindications to the procedure may include a poor life-expectancy of <1 year, multiple metastases, or difficult treatment due to the size or location of tumour. In general, tumours of >5 cm or those in the hilum, the proximal ureter or central collecting system, are not typically recommended for RF ablation [15]. Absolute contraindications include irreversible coagulopathies or severe medical instability such as sepsis.

Clinical studies reported in 2002 and 2003 included 159 patients and are reviewed and discussed in [15]. The mean follow-up of these patients was 2–17 months, the mean tumour size 1.7–3.5 cm, and the success rates per CT follow-up 79–100%. Complications reported included ureteric strictures, thermal injury to the liver and the psoas muscle, perirenal haematomas, and a skin metastasis at the electrode-insertion site. Although the reported complication rates are low even in high-risk patients, greater multicentre experience is required to define complication rates. Also, studies showing the long-term efficacy of RF ablation of RCC are still needed to define appropriate indications and treatment outcomes.

EFFICACY OF SURGERY FOR TREATING METASTATIC RCC

Of patients with RCC, 30–40% present with metastatic disease at first diagnosis, and another 30–50% with initially organ-confined disease will develop systemic tumour dissemination, regardless of initial surgical treatment. Whereas localized (T1 or T2) RCC is curable by resecting the tumour-bearing kidney, thereby achieving a long-term survival rate of ≈80%, there is currently no effective systemic treatment for metastasized RCC that promises to substantially improve the patients’ clinical prognosis [16]. After using an adjuvant systemic therapy, response rates of only 15–22% can be expected.

Whereas for patients with unresectable metastatic disease removal of the primary tumour combined with an adjuvant systemic treatment slightly improves the patients’ clinical prognosis [17,18], complete surgical resection of synchronous or metachronous metastatic lesions is, if possible, strongly recommended as the most effective therapeutic approach.

As reported by Kierney et al. [19] complete metastasectomy in 77 advanced-stage patients resulted in a favourable long-term survival rate of 59% and 31% at 3 and 5 years, respectively, indicating a better clinical outcome from surgery than the median long-term survival of 27 months for conservative management [19,20]. Subsequently, the question of whether surgical resection of RCC metastases can be considered as causing acceptable therapy-related morbidity that, in addition, also improves the patients’ clinical prognosis and/or quality of life was repeatedly addressed. Attempts were also made to identify prognostically relevant variables, e.g. location of metastatic lesions, that could be correlated with the clinical prognosis of an individual patient treated by surgery for metastases from RCC.

Kierney et al. [19] reported on 36 patients with solitary metastases either within the lungs, the brain, the thoracic walls or the abdomen, who had a metastasectomy provided they remained disease-free for at least 27 months after a tumour nephrectomy as initial treatment; 77% survived for >1 year, with 31% of them still being alive after a follow-up of 5 years.

A retrospective analysis included 278 patients with RCC, of whom half had a complete resection of metastases at different locations [16]. After complete or incomplete metastasectomy, the 5-year survival rate was 44% and 14%, respectively. Interestingly, even resecting a second or third tumour recurrence did not significantly worsen the clinical outcome.

Han et al. [20] reported on 297 patients with metastasized RCC (solitary pulmonary metastases in 120; solitary skeletal metastases in 33; metastatic lesions at multiple locations in 144). After resecting solitary metastases, there was a comparable long-term survival of 27 months for patients with either pulmonary or bone metastases. The response rates to systemic adjuvant treatment were 44% and 20% for patients with lung or bone metastases, respectively, and had no substantial impact on the patients’ long-term survival [20].

Swanson et al. [21] tried to determine whether metastasectomy could improve the clinical prognosis of 179 patients with only solitary metastases within the lungs (50 patients), bones (56), visceral organs (23) or brain (23). Synchronous metastases already present at the time of tumour nephrectomy significantly impaired the clinical outcome when compared with patients developing metachronous metastatic spread (long-term survival rate 22% and 39% for synchronous and metachronous metastatic spread, respectively).

In an investigation that included 101 patients who had a total of 152 surgical interventions to resect metastatic lesions from RCC at different locations, the median long-term survival was 28 months for the entire cohort [22]. In contrast to the number of repeated resections, the presence of solitary vs multiple metastases, and tumour stage and size at initial diagnosis, only the possibility of repeat metastasectomy was associated with a more favourable clinical prognosis [22]. As
previously indicated [16], a disease-free interval of >2 years after tumour nephrectomy was associated with a better disease-specific survival.

However, for these cited studies it remains to be clarified whether or not the location of the resected metastases, e.g. in the lungs, bones or at visceral organ sites, has any effect on the patients’ clinical prognosis.

**CLINICAL PROGNOSIS AFTER RESECTING PULMONARY METASTASES**

Friedel et al. [23] reported on 5206 patients with pulmonary metastases from primary tumours of different origin. The 5- and 10-year survival rates were 36% and 26%, and 13% and 7% after a complete metastasectomy. By multivariate statistical analysis, a disease-free interval of ≥36 months after nephrectomy and the presence of only solitary metastases were identified as independently predicting the clinical outcome after therapy.

Fourquier et al. [24] treated 50 patients with pulmonary metastases (solitary in 19; multiple unilateral and bilateral in 13 and 18) with a metastasectomy. The 5-year survival rate was 44% and 22% after complete vs incomplete resection of metastatic lesions.

As reported by Pfannschmidt et al. [25], complete resection of metastases was possible in 145 of 191 patients with RCC metastasized to the lungs. The 5-year survival rate was 42% and 22% after a complete or incomplete metastasectomy. Synchronous regional lymph node metastases decreased the 5-year survival rate to 24%. The number of metastases resected from the lungs had a significant effect on the patients’ long-term survival (5-year survival rate 47% vs 15% after resecting of <7 or ≥7 metastatic lesions, respectively). In concordance with Cerfolio et al. [26], a multivariate statistical analysis identified the number of pulmonary metastases (< or ≥7), the presence of regional lymph node metastases, and a complete metastasectomy in addition to the duration of the recurrence-free survival after initial treatment (< or ≥23 months) as patient characteristics of independent prognostic importance.

In conclusion, a 5-year survival rate of ≥38% can be expected after completely resecting pulmonary metastases from RCC (Table 1) [24–31], thereby confirming the superiority of this treatment over conservative management. In this context, the surgical method selected, either in form of segmentary resection or pneumonectomy, had no effect on the patients’ long-term survival.

**RESECTION OF BONE METASTASES**

Jung et al. [32] reported on 99 patients with solitary (26) or multiple (47) bone metastases (synchronous in 49). Patients undergoing complete resection of a solitary lesion remained continuously free of disease (median follow-up 69 months). Althausen et al. [33] followed 38 patients with metachronous bone metastases; the long-term survival rates at 6 and 12 months and 5 and 10 years after complete resection of solitary lesions were 90% and 84%, and 55% and 39%, respectively. Clinical characteristics identified that affected the duration of recurrence-free survival were a long disease-free interval since initial surgery, and the presence of solitary, peripheral metastases. As reported by Kollender et al. [34], the 3-year survival was 38% using a broad and complete excision of osseous lesions at different locations.

Sundaresan et al. [35] reported a significant improvement in neurological symptoms in most patients having surgery for bone lesions to decompress the spinal cord. Les et al. [36] compared the clinical efficacy of surgery with that of a limited conservative approach. Whereas the median long-term survival was 36 months for surgically treated patients, the life-expectancy decreased to 20 months for conservative therapy.

**RESECTION OF LIVER METASTASES**

The presence of hepatic metastases in patients with RCC is associated with a poor clinical prognosis. However, solitary liver metastases with no simultaneous presence of metastatic deposits at other organ sites is rare. Therefore, only few clinical data on the value of liver surgery for metastasized RCC are presented.

Göring et al. [41] reported on 42 patients either treated by surgical resection or cryoablation of solitary liver metastases from solid tumours of different origin. With an average long-term survival of 45 months, the survival rates after the latter approach were 55% and 39% at 3 and 5 years of follow-up, respectively. There was no significant effect of the respective treatment on the clinical outcome; the 5-year survival rate after surgery or cryoablation was 40% and 37%, respectively. In contrast, as reported by Lang et al. [42], the 5-year survival rate hardly exceeded 16% after surgical resection of liver metastases from different solid primary malignancies.

In our series [43], 17 patients with metachronous liver metastases from RCC had...
surgery; metastasectomy was feasible in 13 patients, with right hemi-hepatectomy in nine (three multivisceral resections), wedge resection in four and ex situ (mobilization and eversion from the abdomen) resection in one. Full resection was possible in 11 of 13 patients. The mean survival in unresectable disease was 4 months, which increased to 16 months after complete removal of metastatic lesions.

In summary, the presence of hepatic metastases in patients with RCC is associated with a poor prognosis, mainly because they have a high tumour load and additional metastatic deposits at other organ sites (Table 3) [43–48].

### RESECTION OF BRAIN METASTASES

The mean long-term survival of patients left untreated for brain metastases is 3 months. Currently available treatments include radiotherapeutic (γ-knife or whole-brain radiation) and surgical approaches. For 90 patients with brain metastases, 26 and 64 of whom were either treated by radiotherapy or surgery, Pomer et al. [49] reported a 1-year survival rate of 31% and 15% after surgery or radiotherapy, respectively. Wronski et al. [50] reported on 709 surgically treated patients with brain metastases; when compared with the clinical prognosis of conservatively treated patients, the survival rate of 51% at 1 year and 24% at 2 years appeared much more favourable. In the latter series, invasion of the cerebellum, that decreased the median long-term survival to only 3 months, was identified as the most important adverse prognostic factor.

Badalament et al. [51] operated on 20 patients with brain metastases, with adjuvant radiotherapy being used in most. In concordance with Shibui et al. [52], the combined treatment was the most effective approach, resulting in a mean long-term survival of 21 months.

Harada et al. [53] reported on 12 patients with brain metastases from RCC treated by surgery; whereas adjuvant radiotherapy was used in seven, another six remained untreated as their general health was worse. With a mean long-term survival of 10 months, two-thirds of patients either treated by surgery alone or surgery with radiotherapy were still alive after 1 year of follow-up (with five surviving at 3 years). In contrast, none of the conservatively treated patients survived for >1 year after initial diagnosis. In an investigation by Siebels et al. [54], there was local tumour control and relief from neurological symptoms in 95% and 70% of patients treated with a γ-knife.

In concordance with observations for RCC metastasized to the liver, the poor clinical prognosis associated with brain metastases reflects the patients’ advanced tumour stage. However, in selected cases, an aggressive therapeutic approach by surgery with or without additional radiotherapy results in a greater life-expectancy. However, the main aspect of treating CNS lesions is the improvement in neurological symptoms and overall quality of life.

### SURGICAL TREATMENT OF LOCAL RECURRENCE

Incomplete resection at the time of initial RN or NSS increases the risk of local recurrence. The likelihood of subsequently developing local recurrences is 1–14% [55–58]. Whereas locally recurrent disease after surgery for solid malignancies usually reflects an unfavourable clinical prognosis, thereby questioning the value of secondary surgery, alternative therapeutic options with at least some clinical efficacy are not available for RCC. Therefore, surgical resection of local recurrences from RCC is considered the treatment of choice. However, information on the clinical benefit of this approach is sparse, because relapses from RCC confined to the renal fossa are rare.

The largest series reported so far included 1737 patients treated by tumour nephrectomy; locally recurrent disease was detected in 2% within the first 5 years of follow-up [56]. Surgical therapy significantly improved the 5-year survival rates when compared with a systemic immuno- (chemo-) therapy, at 51% and 18% for surgery and conservative treatment, respectively.

Subsequent studies reported a long-term survival rate after surgical treatment for local recurrences as 40–45% [55,59]. Tanguay et al. [60] reported a 2-year survival rate of 80% for 15 patients who had a complete resection of locally recurrent RCC. In contrast, Frydenberg et al. [61] suggested combined intraoperative radiation and surgery as the most effective treatment. The median long-term survival was 29 and 42 months in patients treated by

<table>
<thead>
<tr>
<th>Ref</th>
<th>N patients</th>
<th>Survival, %</th>
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<tbody>
<tr>
<td>[33]</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>[37]</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>[34]</td>
<td>45 (solitary lesions)</td>
<td>38 (&gt;3 years)</td>
</tr>
<tr>
<td>[32]</td>
<td>99</td>
<td>100 (wide excision, solitary lesion)</td>
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<td>[38]</td>
<td>42</td>
<td>10</td>
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<tr>
<td>[35]</td>
<td>30</td>
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<td>[40]</td>
<td>45</td>
<td>54</td>
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<tr>
<td>Mean</td>
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<thead>
<tr>
<th>Ref</th>
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<th>Survival, %</th>
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<tbody>
<tr>
<td>[43]</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>[44]</td>
<td>3</td>
<td>12/21 for 2 followed</td>
</tr>
<tr>
<td>[45]</td>
<td>12</td>
<td>5 patient disease-free for 6–56</td>
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<tr>
<td>[46]</td>
<td>28</td>
<td>21</td>
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<td>[47]</td>
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<td>26</td>
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<td>[48]</td>
<td>4</td>
<td>33 *median.</td>
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<th>Table 2</th>
<th>The clinical outcome after surgical resection of bone metastases originating from RCC</th>
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<tr>
<td>Ref N patients</td>
<td>Survival, 3-year, %</td>
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<tr>
<td>[43–48]</td>
<td>1 year after initial diagnosis. In an investigation by Siebels et al. [54], there was local tumour control and relief from neurological symptoms in 95% and 70% of patients treated with a γ-knife.</td>
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<tr>
<th>Table 3</th>
<th>The clinical outcome after surgical resection of liver metastases originating from RCC</th>
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<tr>
<td>Ref N patients</td>
<td>Survival, 3-year, %</td>
</tr>
<tr>
<td>[43–48]</td>
<td>Long-term, months</td>
</tr>
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surgery alone or surgery plus radiotherapy, respectively, clearly favouring the combined therapy.

From such data, an aggressive surgical approach, regardless of possible therapy-induced morbidity [56,60], promises (when compared with conservative treatments) to significantly improve the clinical prognosis of patients with locally recurrent RCC (Table 4) [55,56,59,62,63]. Whether an additional systemic treatment in the form of immunotherapy or chemotherapy provides further clinical benefit remains to be determined.

CONCLUSION

Of patients with RCC, 30–40% present with metastatic disease at first diagnosis, and another 30–50% with organ-confined RCC will develop systemic tumour dissemination regardless of the initial surgical treatment. Once distant metastatic spread has been established, the significant treatment challenge results from pronounced resistance of RCC to both chemotherapy and radiotherapy [64]. Although the presence of only pulmonary metastases is associated with a more favourable clinical prognosis than for patients with metastases at other sites, the data presented here clearly show that in selected cases, surgical treatment even of extra-pulmonary metastases can significantly improve the patients’ quality of life and life-expectancy.

Several patients characteristics have been identified as predicting a more favourable outcome after surgery; these include: solitary lesions of small diameter, complete resection, a disease-free survival of >2 years after initial treatment, the absence of neurological symptoms if there are brain metastases, restriction of metastatic disease to one organ site, the possibility of a second or third resection even after the repeated development of recurrent disease, and a Karnofsky Index of >70. These variables must be considered to weigh possible therapy-induced morbidity and mortality against the clinical benefit. There is significant evidence in favour of the surgical management of metastasized RCC in patients presenting with resectable disease. Whenever possible, surgical management should be used in these patients, but considering the quality-of-life aspects.

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Number of metastatic sites rather than location dictates overall survival of patients with node-negative metastatic renal cell carcinoma. *Urology* 2003; 61: 314–9


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Abbreviations: NSS, nephron-sparing surgery; RN, radical nephrectomy; RF, radiofrequency.
The immunotherapy of prostate and bladder cancer

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The role of the immune system in controlling the growth of tumour cells is highly complex and has been extensively debated. It is well documented that the immune system controls virally induced cancers, and there is evidence for a role of specific immunity in other types of tumours. The greater understanding of the regulation and optimization of adoptive, specific immune responses, and the better characterization of tumour-associated antigens indicate the way for active specific vaccination and cell therapy in urological tumours. Currently, bacille Calmette Guerin immunotherapy is established for localized bladder cancer and many experimental immunotherapies are under evaluation. Here we review some timely aspects of tumour immunology, and describe the current status and development of immunotherapy in prostate and bladder cancer.

TUMOUR IMMUNOLOGY

The first defence against intruding microbes and xenographs is harnessed by the innate immune system, which includes the complement and coagulation systems, defensins, different phagocytes including dendritic cells (DCs), and natural killer (NK) cells. DCs are key professional antigen-presenting cells and can activate both innate NK cells and the naive and memory CD4+ and CD8+ T cells of the adaptive, specific immune system. In this ‘immunological synapse’, DCs present antigenic peptides to T cells and provide the critical co-stimulatory molecules (e.g. CD80/86, CD40, OX40L, interleukin-12) and adhesion molecules needed for optimal T cell activation (Fig. 1A). DCs exist as two main phenotypes, immature DCs specialized in antigen uptake, and mature DCs, adapted for antigen presentation. The major effector cell that mediates the rejection of solid tumours in preclinical animal models is the cytolytic T lymphocyte (CTL). CTLs are derived from naive or memory CD8+ T cells. Each CTL expresses a clonotypic T cell receptor (TCR) that confers specificity for a given target antigen. Antigens recognized by TCRs on CD8+ T cells consist of 9–11-amino acid peptide fragments bound to the MHC class I molecules on the surface of the antigen-presenting cell or the tumour target cell. The peptides displayed by MHC class I molecules are generally, but not exclusively, derived from endogenous proteins made by the antigen-presenting cell. A process called ‘cross-priming’ may also allow external proteins to be presented via the class I pathway. Therefore, to initiate CTL responses against cancer cells, apoptotic bodies or necrotic material derived from tumour cells need to be taken up, processed and presented by the DC in the draining lymph nodes. Peptides derived from tumour-associated antigens (TAA) are then presented by MHC class I and class II molecules on activated DCs to CD8+ and CD4+ T cells, respectively. For a recent review on tumour immunology and tumour cell recognition by the immune system, see [1].

FACTORS REGULATING ANTI-TUMOUR IMMUNITY

T HELPER CELLS

There is substantial evidence that T cells can recognize TAAs in man, and that this T cell immunity must be boosted to be clinically relevant. At least in vivo, both the effective activation of naive CD8+ T cells and the generation of long-lived memory CTLs require assistance by antigen-specific CD4+ T helper (Th) cells which secrete interleukin-2, interferon-γ and other Th1 type cytokines. Th cells produce interleukin-2, which is the main factor for growth and maintenance of CTLs. Antibody responses to tumours, which are promoted by CD4+ T cells of the Th2 type, are thought to be less important in vivo. The TCRs of CD4+ T cells recognize 12–20-amino acid TAA peptides bound to MHC class II molecules on the DC. Such peptides typically derive from extracellular proteins taken up by the DC (Fig. 1A).

THE DIFFERENTIATION STATUS OF DC

Immature DCs lack co-stimulatory signals and mediate T cell tolerance rather than T cell activation. Intruding microbes express ligands which bind to pattern recognition receptors such as toll-like receptors (TLRs) on DCs and induce their maturation by inducing inflammatory cytokines such as granulocyte macrophage-colony stimulating factor (GM-CSF), TNF-α and interleukin-1. These ‘danger signals’ link innate to adaptive immunity, and are central in eradicating foreign pathogens. CD4+ T helper cells also induce maturation of DCs through cross-talk via CD40L–CD40 interaction (Fig. 1A).

CD25+ CD4+ regulatory T cells (T-reg) are important for maintaining immunological tolerance; they also exert an inhibitory effect on CD4+ and CD8+ T cell responses against cancer [2]. Systemic depletion of T-reg cells with anti-CD25 antibody or immunotoxin before adoptive transfer of antigen-specific T cells may have implications for cancer immunotherapy. However, CD8+ and CD4+ effector T cells also express CD25 transiently upon activation, and depletion of these cells during the acute phase of an antitumour T cell response may limit the use of this approach. Moreover, an indiscriminate broad depletion of T-reg cells might precipitate autoimmunity. It was recently shown that TAA-specific CD25+CD4+ T-reg cells are present at tumour sites (Fig. 1B) [3]. T-reg cell depletion in the clinic will probably await methods which preferentially deplete those T-reg cell subsets suppressing...
Necrotic or apoptotic tumour cells thus preventing CD8+ class I molecules is lost on metastatic cells. Frequently, the surface expression of MHC processing/presentation machinery, regulation of the tumour cell antigen include loss of TAA expression and down-regulation by the immune system. These mechanisms to evade detection and Tumour cells have developed several immune escape mechanisms to protect themselves from the immune system. One of these mechanisms is the release of immunosuppressive molecules such as TGF-β, which are detrimental for CTL activity.

**OPTIMIZING CO-STIMULATION**

The rather low tumour response rates obtained so far with DC-based cancer vaccines may partly be due to the use of immature DCs, and to a lack of danger signals in the tumour environment. TLRs may be used to develop cancer immunotherapy strategies that mimic the efficient immune responses to pathogens. For example, CpG ODNs with unmethylated CpG motifs, abundant in viral and prokaryotic genomes, can trigger an immunomodulatory cascade in humans involving B cells, T cells, NK cells and DCs. The adjuvant response of CpG ODNs triggering TLR-9 skews the immune system in favour of a Th1-type response and pro-inflammatory cytokine production. The inclusion of CpG ODNs as vaccine adjuvants has shown promising results in animal models, including bladder cancer. Tumour-specific antibody–cytokine fusion proteins have been used to target Th1-like cytokines to the tumour micromilieu, thereby improving the outcome of antitumour vaccination. Double-stranded RNA, a major viral signature, activates DCs via TLR-3 or cytosolic double-stranded RNA-binding enzyme protein kinase R. This activation leads to secretion of interleukin-12 and type-1 interferons, which are important cytokines linking innate and adaptive immunity. Effective activation, differentiation and interleukin-12 secretion of DCs is also achieved by CD40L ligation of its counter receptor CD40 on DCs. Cells can either be exposed to soluble CD40L trimer or transduced by an adenoviral vector expressing CD40L, followed by antigen loading. Direct injection of such vector into experimental tumours can effect impressive antitumour responses in vivo.

**ADOPTIVE T CELL TRANSFER**

This encompasses the use antigen-loaded DCs for expanding CTLs in vitro, followed by reinfusion of the custom-made CTLs into the patient. T lymphocyte cultures are repeatedly stimulated with autologous DCs modified to present the antigen to the DCs and then re-infused into the patient. This approach has shown some success in clinical trials, but the efficacy is variable and the treatment is not without potential side effects.

**IMMUNE ESCAPE MECHANISMS**

Tumour cells have developed several mechanisms to evade detection and eradication by the immune system. These include loss of TAA expression and down-regulation of the tumour cell antigen processing/presentation machinery. Frequently, the surface expression of MHC class I molecules is lost on metastatic cells, thus preventing CD8+ T cells from recognizing their target. On the other hand, NK cells can kill MHC class I-negative target cells and may act as surrogate effectors. Tumour cells release immunosuppressive molecules such as TGF-β, interleukin-10 and prostaglandins. Therefore, the tumour micromilieu is usually dominated by Th2 cytokines and T-reg cells which are detrimental for CTL activity. TGF-β was recently shown to convert CD4+ effector T cells into T-reg cells. Finally, tumour cells may up-regulate protective anti-apoptotic molecules, or express surface Fas ligand which induces apoptosis of attacking CTLs.

**ANTITUMOUR RESPONSES**

However, promising results are reported in melanoma using lymphodepletion with cyclophosphamide plus fludarabine. Antitumour responses are driven by CD8+ T cells, which recognize tumour antigens presented by MHC class I molecules on the surface of tumour cells. These CD8+ T cells can be expanded in vitro and re-infused into the patient. This approach has been successful in some patients with advanced melanoma, but the response rates are low and the treatment is not without potential side effects.

**OPTIMIZATION OF DC- AND T CELL-BASED IMMUNOTHERAPIES**

DC-based therapies

Immature DCs can readily be generated from peripheral blood monocytes with interleukin-4 and GM-CSF, and can be matured with TNF-α or other stimuli. Immature DCs can be loaded with the full-length antigen in the form of a recombinant protein, in vitro transcribed mRNA encoding the antigen, or a viral vector comprising the cDNA encoding the antigen. DCs are then matured for optimal processing and presentation of peptide epitopes. Alternatively, fully mature DCs can be pulsed with custom-made synthetic MHC class I-restricted peptides for direct presentation of known immunogenic epitopes. Autologous antigen-modified mature DCs may be infused as a vaccine into patients with cancer. Clinical trials using DC vaccines against tumours show that they are safe. The results have been variable, with long-lasting clinical responses in some studies.
present immunogenic TAA epitopes. Specific CTLs with high avidity for an antigenic epitope can be identified by binding of TCRs to fluorescent peptide/MHC tetramers, or by interferon-γ/TNF-α release using ELISA technologies. T cell clones can be raised from a single T cell, or a specific T cell population can be isolated by fluorescence-activated cell sorting using peptide/MHC tetramer molecules. Isolated lymphocyte cultures can be expanded to clinically relevant numbers for adoptive transfer back to the patient. In contrast to early studies of adoptive therapy that used lymphokine-activated killer cells or tumour infiltrating lymphocytes (TILs), antigen-specific T cell clones for adoptive transfer provide effector cells of uniform specificity and phenotype that retain physiological responses stimulus with antigen and low-dose interleukin-2 [15]. T cells are expanded ex vivo, thereby avoiding the immunosuppressive environment of the tumour-bearing host. Further, the patient can receive partial myeloablation before T cell transfer. This lymphodepletion creates space and provides homeostatic lymphocyte survival and proliferative signals for the adoptively transferred T cells [16]. Priming with low-dose cyclophosphamide has been known for decades to boost immune responses to antigens. Interestingly, it was recently shown that cyclophosphamide selectively reduces T-reg cell numbers and function [17]. Rosenberg et al. [4] reported a ≥51% objective responses in patients with therapy-resistant metastatic stage IV melanoma treated with adoptive TIL transfer plus high-dose interleukin-2 after in vivo lymphodepletion with cyclophosphamide and fludarabine. Experimental studies in mouse models showed that removing T-reg cells probably contributes to these dramatically improved results [18].

### PROSTATE CANCER

Prostate cancer is a leading cause of illness and death among men in Western countries. Current statistics from the American Cancer Society estimate that 232,090 men will be diagnosed with prostate cancer and that 30,350 will die from this disease in the USA in 2005 [19]. The current standard therapies used for organ-confined prostate cancer include radical prostatectomy, external beam irradiation and brachytherapy, under some circumstances incorporating neoadjuvant or adjuvant hormonal therapy [20]. While these therapies are relatively effective in the short term, a significant proportion (30–40%) of patients having initially localized disease will ultimately relapse [21]. For metastatic prostate cancer the main therapy is androgen ablation. While this provides cytoreduction and palliation, progression to hormone-refractory disease typically occurs within 14–20 months. Many clinical studies have been reported in the field of chemotherapy for advanced androgen-independent prostate cancer. Only recently have two trials revealed that chemotherapy marginally improves the overall survival of patients with hormone-refractory disease [22,23]. Thus, there is a great need for better techniques to treat advanced hormone-refractory prostate cancer, which can complement the standard techniques.

### TUMOUR ANTIGENS ASSOCIATED WITH PROSTATE CANCER

Historically, the prostate gland was considered an immunologically privileged site as initial reports suggested there were no lymphatics; however, this has been found to be erroneous. Evidence for this includes the ability of the prostate to mount inflammatory responses and that a low density of TILs is a predictive factor for a poor outcome [24]. There are many reasons why prostate cancer is particularly well suited for immunotherapeutic approaches. First, as the prostate is not an essential organ, proteins that are specifically expressed by neoplastic and normal prostate cells constitute suitable targets for T cell-based immunotherapy. Second, many genes and proteins with specific or preferential expression in normal prostate and prostate cancer cells have been identified (Table 1), and were recently reviewed by Essand [25]. Third, prostate cancer cells also express many epithelial cancer-related antigens that may also be exploited. Examples include mucins (MUC-1,

### TABLE 1 Tumour-associated antigens in prostate and bladder cancer

<table>
<thead>
<tr>
<th>Cancer/Subgroup</th>
<th>Antigens</th>
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<tbody>
<tr>
<td><strong>Prostate</strong></td>
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</tr>
<tr>
<td>Differentiation antigens with known T lymphocyte-restricted peptide epitopes</td>
<td>PSA; PAP; TARP; Kallikrein-1-4; Prostate; Trp-p8</td>
</tr>
<tr>
<td>Differentiation antigens with potential immunogenicity</td>
<td>Kallikrein-2; prostate-specific transglutaminase (TGM-4); Homeobox NKX3.1; prostate GAGE-like protein-4 (PAGE-4); PDEF; PART-1; PsdR; gene differentially expressed in prostate (GDEP); C-terminal tensin-like protein (Cten); PATE; PEDT; STAMP-1; AlbZIP HPG1; NGEP</td>
</tr>
<tr>
<td>Overexpressed antigens with known T lymphocyte-restricted peptide epitopes</td>
<td>PSMA; PSCA</td>
</tr>
<tr>
<td>Overexpressed antigens with potential immunogenicity</td>
<td>Six transmembrane epithelial antigen prostate (STEAP); PMEPA-1; PSDR-1; PrZL</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td></td>
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<tr>
<td>Shared tumour-specific antigens (cancer testis antigens)</td>
<td>B-antigen; CTL-recognized antigen on melanoma; G-antigen 1, 2, 4–6, 7B, 8; Melanoma antigen-A1-4, 6, 10, 12; New York esophagous 1</td>
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<td>Antigens overexpressed by tumours</td>
<td>α-fetoprotein; cyclophilin B; HER-2/neu (human epidermal receptor-2/neurological); Livin (ML-IAP); MUC-1; renal antigen; renal ubiquitous 1, 2; survivin; survivin 2B (intron 2- retaining survivin)</td>
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<tr>
<td>Tumour antigens resulting from mutations</td>
<td>KIAA0205</td>
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and MUC-2) which both have altered glycosylation when expressed on malignant epithelial and glandular cells. Fourth, immune responses to prostate-related antigens can be considered tumour-specific in patients with recurrent metastases after radical prostatectomy. Fifth, serum PSA levels can be used as a surrogate marker to evaluate clinical responses.

**PROSTATE CANCER VACCINES AND TRIALS**

Many immunogenic peptides derived from the prostate tissue antigens (PSA), prostate specific membrane antigen (PSMA), prostate acid phosphatase (PAP), prostate stem cell antigen (PSCA), kallikrein 4, prostein, trp-p, and TCR\(\gamma\) alternate reading frame protein (TARP) have been identified in vitro. They are restricted by HLA-A2, HLA-A3 or HLA-A24, which are all relatively common MHC class I molecules in the general population. References to the immunogenic peptide epitopes are given in a recent review [25].

T helper cell activation is essential for a sustained immunological response against tumour cells. MHC class II-binding peptides from prostate tissue antigens that can activate CD4\(^+\) T helper cells have so far been identified from PSA, PSMA, PAP, Kallikrein-4 and recently also TARP [26]. Peptides derived from human telomerase reverse transcriptase (hTERT) may be used to expand T cells with activity against a broad spectrum of tumours, including prostate cancer. hTERT peptides restricted by HLA-A2, HLA-A3 and HLA-A24 have been identified, along with various MHC class II-restricted peptides.

Several phase I and phase II clinical trials have been conducted with autologous DCs pre-loaded with prostate tissue antigens. Murphy et al. [27–29] were the first, using DCs pulsed with HLA-A2-restricted PSMA peptides. Burch et al. [30] and Small et al. [31] used DCs pulsed with a recombinant fusion protein composed of PAP linked to GM-CSF (APC8015, Provenge), while Fong et al. [32] used DCs pulsed with murine PAP. Heiser et al. [33] used DCs transfected with mRNA encoding PSA, while Barrou et al. [34] used DCs pulsed with recombinant PSA. Furthermore, Vonderheide et al. [35] recently reported a phase I clinical vaccination trial with autologous DCs pulsed with an HLA-A2-restricted hTERT peptide. hTERT-specific T lymphocytes were induced in four of seven patients with advanced breast or prostate carcinoma, as assessed by peptide/MHC tetramer, enzyme-linked immunospot, and cytotoxicity assays. Immunotherapy studies based on Provenge have been evaluated in phase II [36] and phase III [37] clinical trials for metastatic androgen-independent prostate cancer. Provenge was well tolerated, with grade 1 and grade 2 fever chills as the most common side-effect. Patients with advanced prostate cancer and a Gleason score of \(\leq 7\) who were treated with Provenge had a median survival of 30.7 months, in comparison with patients treated with placebo, who had a median survival of 22.3 months, i.e. a median survival of 8.4 months longer in patients receiving Provenge. Similarly, the time to progression and emergence of cancer-related pain was longer in the treatment group [37]. There was no benefit in men with Gleason scores of \(>8\).

Generally speaking, the DC vaccination trials for prostate cancer have been safe and well tolerated by the patients. Immunological responses were limited but there were specific T cell responses in some patients, showing that it is possible to activate CTLs against self-antigens such as PSA, PSMA, PAP and hTERT in vivo in a clinical setting.

Adaptive transfer of prostate antigen-reactive CTLs have not yet been tried in patients with prostate cancer. However, our laboratory recently showed that potent CTLs directed against the prostate tissue antigen TARP [38,39] can be generated ex vivo by repeated stimulation of lymphocyte cultures with autologous peptide-pulsed DCs followed by peptide/MHC tetramer-guided sorting of the stimulated T cells and 1000-fold rapid expansion of the sorted T cells [40]. The sorted and expanded T cells retained both specificity and activity, showing that large numbers of prostate tissue antigen-specific CTLs can be generated ex vivo for adoptive transfer to patients with prostate cancer [40]. Alternatively, the molecular characterization of TAA epitopes and the TCRs that recognize them has opened up the possibility to genetically engineer autologous T cells ex vivo to express a full-length TCR or a chimeric single-chain Fv receptor that is specific for a TAA epitope [41]. T cells against PSMA were recently generated using such an approach [42].

**BLADDER CANCER**

Urinary bladder cancer is the fifth most common malignancy among men in the Western society, but is three times less frequent among women; most patients are \(>65\) years old. Urothelial TCCs are either superficial or muscle-invasive, and \(>70\%\) of cases present with superficial tumours. Superficially growing tumours can be removed by transurethral resection; with this approach, long-term survival is achieved in \(\approx 80\%\) of cases, but less than half are cured. New tumours arise after resection, and to prolong the tumour-free intervals, resection is combined with cytostatic drugs or attenuated BCG instillation. Cystectomy may save patients with infiltrating tumours, but the prognosis is grim for patients with metastases. Therefore, there is a need to develop alternative therapies.

**TUMOUR ANTIGENS ASSOCIATED WITH BLADDER CANCER**

Tumour antigens can be used for detecting bladder cancer growth, targeting radionuclides or chemotherapeutic drugs to tumour tissue, and for evoking tumour-specific immune responses. Bladder cancer has been associated with several TAAs (Table 1). MAGE-A is expressed in superficial tumours, whereas only half of infiltrating bladder carcinomas were positive [43]. PSCA was originally thought to be specifically expressed by prostate epithelial cells, but recent studies show that PSCA is also expressed in normal urothelium, oesophagus and stomach [44]. The reports on PSCA in undifferentiated muscle-invasive bladder cancer have been contradictory, while PSCA is regularly expressed in differentiated superficial tumours. Other antigens associated with bladder cancer are mutated variants of tumour suppressor genes (p53, Rb) or oncogenes (c-H-ras, c-myc, HER-2/ neu). Alterations in these genes are mainly associated with tumours of higher stage and/or grade [45]. Recently, the cancer-testis antigens NY-ESO-1 and LAGE-1 were shown to be expressed in 48% of high-grade and 14% of low-grade TCC tumours [46]. There are few examples of bladder cancer-specific antigens. A group of nuclear matrix proteins was isolated from patients with bladder cancer; of these, bladder cancer-4 appears to be a clinically useful marker [47].

**BCG IMMUNOTHERAPY**

Because of the Th2 suppressor cytokine profile which dominates the tumour milieu, bladder cancer could be susceptible to immune therapy, tilting the profile into Th1.
To this end, intravesical treatment with live attenuated BCG is a well-established immunotherapy in bladder cancer. BCG therapy causes a significant reduction in relapse rate, prolongs the progression-free interval and has become a standard treatment, particularly for patients with carcinoma in situ (CIS). The complete response rate is 70–75% and there are remissions within a 5-year period in 70% of patients [48]. BCG causes a local inflammation in the bladder wall and its therapeutic efficacy relies on a normally functioning immune system. It is likely that CpG sequences in the bacterial genome are important in triggering TLR-9 receptor-positive cells of the innate immune system. Immune responses can be monitored by the release of several urinary cytokines. The cytokine profile reflects that of a Th1 response, but no immunological memory is detected in animal models [49]. Indeed, with longer monitoring the Th1 cytokine profile dominated by interferon-γ and interleukin-12 deviates toward a Th2 profile with interleukin-10 [50]. Human in vitro studies provide strong evidence that BCG is a very potent activator of NK cells, which could explain the strong local response in the absence of systemic immunity [51]. Another study showed that CD4+ T cells and γδ T cells accumulated in the bladder wall after repeated BCG instillations in patients with superficial TCC, while CD8+ T cells and NK cells did not [52]. Moreover, BCG is inefficient in activating tumour-specific CTLs in experimental models [49]. Failure of BCG treatment in advanced disease could thus reflect the inability of this therapy to activate CTLs. BCG is a crude attenuated bacterial suspension which mainly activates innate immunity. To develop immunological memory and systemic immunity, the adaptive system with tumour-specific CTLs needs to be engaged.

CLINICAL TRIALS WITH NOVEL IMMUNOTHERAPIES

Recombinant interleukin-12 has been used intravesically in a phase I study on patients with superficial bladder tumours. Cohorts of three patients received weekly interleukin-12 at five doses of 5–200 μg for 6 weeks. There was no systemic toxicity but there were local adverse events, e.g. dysuria, pain, haematuria and chills. At these doses, patients with tumour lesions had persistent disease. However, seven of 12 patients with no lesions before treatment remained disease-free during a 4-week follow-up [53]. TNF-α has also been used to treat bladder carcinoma but its use is limited by toxicity. Phase I-III studies suggest efficacy also in refractory superficial bladder cancer [54]. Recently, Giannopoulos et al. [55] reported on patients with superficial tumours who had the tumour resected followed by intravesical treatment with recombinant interferon-γ. Of 60 patients so treated, 74% remained tumour-free during a follow-up of 26.5 months, compared to 52% of patients who received mitomycin C.

Treatment with interferon-α2B has produced modest responses in bladder cancer. This cytokine has been used in combination with BCG therapy to improve T cell responses, as adding interferon-α2B to in vitro cultured immune cells from BCG-treated patients inhibited interleukin-10 production while enhancing interferon-γ [56]. The combined therapy showed low toxicity and was well tolerated. However, 64% of the patients had tumour recurrence at the 5-year follow-up [57]. Bropirimine (an aryl pyrimidine) has been tried in patients with CIS as an oral agent which has a broad spectrum of immunostimulatory activity, mainly activating B cells, NK cells and macrophages. Bropirimine induced a complete response in 20 of 33 patients, but four responders relapsed [58]. The intratumour immune profile in bladder cancer is dominated by Th2-like cytokines such as interleukin-4, interleukin-10, TGF-β and the presence of T-reg cells [59]. In our studies, human bladder cancer biopsies expressed mRNA copies of typically Th2-type cytokines such as TGF-β and interleukin-10, but lacked Th1-type cytokine expression (Loskog et al., unpublished data). Kastelan et al. [60] showed that lymphocytes from patients with superficial carcinoma had lower reactivity to mitogens than controls; moreover, NK cell activity was decreased. Patients with high-grade tumours and/or invasive disease had even lower lymphocyte reactivity. These data indicate that patients with bladder cancer have tumour-associated immunosuppression. Other types of immune escape linked to bladder cancer include a greater expression of apoptosis inhibitors cFLIP and PI-9 in biopsies from bladder cancers (Loskog et al., unpublished data), and down-regulation of the death receptor Fas in bladder cell lines [61]. These findings imply that bladder cancer cells may have a high resistance to apoptosis and a forceful immune attack is needed to overcome these barriers.

Bladder cancer is an attractive candidate for innovative therapies such as gene and immunotherapy because the bladder is accessible. Administration of the Th1-initiating molecule CD40L (viral vector gene therapy) and interleukin-12 (recombinant protein or viral vector gene therapy) has been used successfully in murine models of bladder cancer [14,62,63]. Such immunogene therapy has been potent in eradicating established tumours in small-animal models and in clinical trials [64,65]. Treating tumours with CpG ODNs has shown potent antitumour responses in animal models. In our studies, CpGs given intravesically in an orthotopic MB49 mouse model cured the mice and stimulated systemic immunity [11]. CpGs could be a good candidate for replacing BCG therapy, e.g. human DCs stimulated with BCG induced interleukin-12 and interleukin-10 production, showing a general immune response with both Th1 and Th2. However, CpG ODNs induced only interleukin-12, showing a focused Th1 stimulatory response [66].

CONCLUDING REMARKS AND FUTURE DIRECTIONS

The rapid increase in the understanding of how effective tumour-specific T cell responses are generated will probably result in novel therapeutic and adjuvant therapies for cancer. Such vaccines and protocols will undoubtedly include the use of antigen-loaded DCs and active measures to revert the immune suppressive mechanisms shown by solid tumours, such as in vivo depletion of regulatory T cells. Most currently published DC-based phase II and III trials report antitumour responses. Urological tumours have clinical and immunological features which render them suitable as targets for innovative immunotherapies, and this will undoubtedly attract the interest of clinicians managing these patients.

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IMMUNOTHERAPY OF PROSTATE AND BLADDER CANCER

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Abbreviations: DC, dendritic cell; NK, natural killer; CTL, cytolytic T lymphocyte; TCR, T cell receptor; TAA, tumour-associated antigen; TLR, toll-like receptor; GM-CSF, granulocyte macrophage-colony stimulating factor; T-reg, regulatory T cell; ODN, oligodeoxynucleotide; TIL, tumour infiltrating lymphocyte; PSMA, prostate-specific membrane antigen; PAP, prostatic acid phosphatase; PSCA, prostate stem cell antigen; TARP, TCRγ alternate reading frame protein; hTERT, human telomerase reverse transcriptase; CIS, carcinoma in situ.
A critical analysis of laser prostatectomy in the management of benign prostatic hyperplasia

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INTRODUCTION
TURP has been the standard treatment for BPH for the past 30 years and is a very reliable and straightforward procedure that offers excellent long-term results [1]. However, when carefully analysing published studies it is evident that TURP can be associated with a relatively high complication rate [2] with an important effect on peri-operative morbidity and postoperative sexual function [3,4]. Therefore, in the last decade a significant effort has been made to develop alternative minimally invasive approaches. In particular, different laser techniques have been used in clinical trials, with the specific aim to reduce overall morbidity, while offering the same long-term functional results [5].

In this review we will mainly focus on holmium laser prostatectomy (HLP), high-powered potassium-titanyl-phosphate (KTP) vaporization of the prostate, high-power holmium laser vaporization of the prostate (HoLAP) and interstitial laser coagulation (ILC). In particular our aim is to critically analyse the available evidence for efficacy and safety of laser prostatectomy and to highlight the current role of these procedures in managing patients with BPH patients.

The advantages, pitfalls and unknown factors of the procedures are also detailed, to achieve a more exhaustive and comprehensive understanding of these diverse promising approaches.

HLP
The use of the holmium laser for treating BPH started about a decade ago and since then increasing evidence of efficacy and safety has accumulated. A recent objective review by Tooher et al. [6] analysed the quality of papers on HLP and holmium laser enucleation of the prostate (HoLEP). For HRP, three randomized controlled studies and one comparative trial were available, whilst for HoLEP, two and one were available, respectively. At present, available data show that HLP appears to be at least as effective as TURP in the short term. Preliminary long-term efficacy and durability data are now becoming available. Westenberg et al. [7] presented their data at the 4-year follow-up comparing TURP and HLP in a randomized study. Of the initial 120 patients, 73 were eligible for the 48-month follow-up (60.8%); in that study the two techniques provided equivalent satisfactory long-term results, with no differences in major morbidity. Furthermore, peri-operative morbidity was lower in the HLP group. HoLEP is also safe for most prostate sizes [8] and is being proposed for larger prostates (up to 200 g) as an alternative both to open prostatectomy (OP) and TURP [9]. In a recently published two-centre study with a 1-year follow-up with prostates of <100 g, Montorsi et al. [10] confirmed the overall safety of the HoLEP technique, reporting 1-year functional results at least as good as standard TURP in terms of relief of subjective symptoms and urodynamic findings, whilst Tan et al. [11] reported that pressure-flow data before and after HoLEP showed that it was better at relieving BOO than was TURP. In all cases, HoLEP took longer than a standard TURP, but was associated with a significantly shorter catheterization and hospital stay. Complications were similar in both procedures. In particular, the impact on erectile dysfunction and retrograde ejaculation seemed to be very similar between the groups. The role of HoLEP was also evaluated as an alternative to OP, where the advantages of reduced blood loss and reduced hospital stay can be of particular interest. Kuntz et al. [12], in a prospective randomized study with 120 patients with prostates of >100 g, reported less peri-operative morbidity with HoLEP than OP via a transvesical approach, with a dramatic reduction in blood loss and consequent blood transfusion rate even with very large prostates. The operation was longer in the HoLEP group, although the time for OP also appeared to be longer than generally reported. The efficacy at the 18-month follow-up was assessed, showing equivalent results and adverse events in the two groups [13–15].

Fraundorfer et al. [16] also showed that HLP may be an attractive alternative to standard TURP in terms of both clinical outcomes and cost-effectiveness at the 1-year follow up. Indeed, they reported a shorter hospital stay for the HLP group than for TURP and this result was coupled with lower nursing requirements, lower irrigant requirements, and absence of blood cross-matching and transfusion rate. The second part of the cost-effectiveness analysis was dedicated to the complication rate and the subsequent unplanned clinic visits and re-admissions. These authors highlighted that the HLP group had a lower overall cost for the entire procedure because there were fewer unplanned events than in the TURP group. In a cost analysis at our department comparing HoLEP and OP it was evident that HoLEP had a significantly lower blood loss with less homologous blood transfusion than OP. Moreover, the significantly shorter catheterization time and hospital stay were in favour of the HoLEP group. Interestingly, the early catheter removal (usually the day after surgery) allowed a dramatically shorter hospital stay after HoLEP, with a significantly greater cost reduction for this procedure than for OP [17]. The reliability of the HoLEP procedure to enable early catheter removal was recently confirmed and it was also proposed as a day-case option in selected patients [18,19].

The accuracy of the cancer-detection rate after both HLP and HoLEP was also assessed [20,21], showing that both thermal and morcellation damage to the tissue does not alter the pathologist’s ability to detect cancer...
even after extensive vaporization, compared to TURP.

**BIPOLAR PLASMA KINETIC VAPORIZATION (KTP)**

The high-power KTP laser uses vaporization energy delivered at rapid pulse energy (60–80 W) using a GreenLight PVP System and a Starpulse quasiconstant wave laser (Laserscope, San Jose, California) emitting green light at 532 nm [22]. The procedure seems safe and although time-consuming can guarantee immediate tissue removal, offering a TURP-like cavity [23,24]. The results of these studies did not confirm the encouraging results in terms of early catheter removal described by Biber and Muir [25] and Sandhu et al. [26], and furthermore did not show a shorter catheterization time and hospitalization than with either TURF or TURP. However, the advantages of this technique include the use of saline as an irrigant, thus reducing potential TUR syndrome, and minimal intraoperative bleeding, while subsequently allowing for good visibility throughout the procedure. This technique represents the latest development in technology for treating BPH, especially for larger prostates, as an alternative to standard TURP. The long-term follow-up is still lacking and thus the durability of the procedure has yet to be assessed. Phase III randomized studies are mandatory for an in-depth evaluation of this procedure [27]. Reich et al. [28] presented an experimental study comparing histological findings and coagulative properties of a new laser vaporization technique using the KTP laser with TURP. The high-power KTP allows the combination of the well-known tissue debulking properties of conventional TURP with the safety profile of laser treatments. However, it seems that less tissue is removed during the KTP procedure. They were able to show greater coagulating properties, as the wavelength (532 nm) is strongly absorbed by haemoglobin, and less penetration of the laser beam into tissue (1 mm) than with the Nd:YAG (10 mm) laser, which reduces tissue damage. Furthermore, the same authors reported the benefits of the procedure on patients at high cardiopulmonary risk, or patients on anticoagulant therapy, confirming the excellent haemostatic properties of the vaporization [24]. The limited follow-up of these investigatory reports prevented an assessment of sexual function after KTP laser therapy to be correctly assessed.

**HoLAP**

Tan et al. [29] reported their long-term results (7-year follow-up) with a side-firing dual-wavelength fibre or end-firing fibre. Unfortunately, only 43% of the patients who had the procedure initially were available for assessment. There was an improvement in flow in 83% of patients and at 7 years of follow-up the AUA score decreased by 7 points from baseline; the re-intervention rate was 15%. The results seemed to indicate that this technique has been superseded by new techniques still using the holmium laser for resection or enucleation. However, this technique can be of use when starting to gain experience with the laser beam and in selected patients with small glands.

**ILC**

ILC is still under development and awaits an accurate assessment. Published data varies in terms of results and mainly derives from uncontrolled and unrandomized studies with a very short follow-up. However, preliminary data suggest a very low intraoperative morbidity, whilst immediate complications after surgery include acute urinary retention and irritative symptoms. Prolonged catheterization (10 days) after the procedure is reported in a high proportion of patients (30–60%) [30], and this seems one of the limiting factors to the diffusion of this procedure in clinical practice. Furthermore, nearly 72% of patients described perineal pain and discomfort at 2 weeks and retrograde ejaculation was reported in up to 11%, with re-intervention at 1 year of 8–15%. A long-term follow-up is still lacking for this procedure, as only one study addressed the results at the 3-year follow-up [31].

**PITFALLS AND UNKNOWN FACTORS IN LASER PROSTATECTOMY**

It is generally considered that there is a significant need for a long-term follow-up, correctly assessed with randomized trials, possibly multicentred, especially for the innovative techniques like bipolar plasmakinetic vaporization. This consideration may be applied to the HoLEP technique, where data are available only up to the 2-year follow-up in two different study groups. An international database aimed at collecting all data available for the scientific community would help to confirm the data that currently make HoLEP such an interesting potential alternative both to TURP and OP. So why do surgeons not change to HoLEP? First, because of the generally good results achieved from standard TURP, traditionally widespread and taught throughout the urological community. Second, the HoLEP technique is probably challenging and difficult to teach at the beginning, as expected for all new endourological procedures, such that it is difficult to learn and not all urologists want to tackle it. An interesting issue is that currently no tutoring for HoLEP is available, and therefore learning the procedure is left to the initiative of interested urologists who have to challenge the apparent risks of the procedure by themselves. From this perspective, correct and continuous mentoring is mandatory [32]. Third, the costs for setting up the whole procedure require accurate planning and needs to include stone treatment. Therefore, more cost-consequences studies underlying the feasibility of developing the laser procedure from scratch, with the equipment, together with easily available assistance from both the European and American community, are important for the widespread adoption of this technique. From this perspective the high-power KTP vaporization of the prostate can offer some inducible advantages for the TURP-friendly urologist, as it is based on a manual technique very similar to the latter, associating the best haemostatic and resection properties of laser and electrocautery, without the hazards of morcellation. However, KTP laser prostatectomy is still time-consuming, the time depending strictly on prostate size and, furthermore, long-term data are yet unavailable [33].

Thus again, when long-term studies evaluating the results after KTP treatment are released, it will be interesting to compare these findings with HoLEP, in a prospective, randomized, possibly multicentred study. These considerations are even more important when considering the increasing interest that the urological community has towards laser treatment and minimally invasive treatments in general for BPH [34].

As already described, the objective of these therapies is to resolve BOO to improve the patients’ overall quality of life and to preserve detrusor function. Although recently defined as coincidental, the causal relationship between BPH and sexual dysfunction seems
to be real [3]. However, the impact of minimally invasive procedures, and in particular with all the different lasers, on sexual function has not yet been clarified [35]. Routine urological practice shows that when correctly questioned, the patient will willingly describe the consequences that either the treatments for BPH have on his daily activities, and on his sexual life. Solely mentioning the presence or absence of ejaculation is not enough to describe the actual change in the patient’s sexual life after surgery. Further studies must carefully analyse the complicated interrelation between LUTS, BPH, sexual function and surgical outcome, to correctly evaluate the impact that each treatment, with its energy source and procedure, has on the patient. These studies necessarily need to be prospective as it is now known that BPH per se is associated with ejaculatory and erectile disorders [36]. Sexual function after laser prostatectomy was assessed by Tuukkanen et al. [4], where there was a significantly more total erectile dysfunction in the TURP group than after laser treatments (contact and hybrid). However, when analysing the data, TURP seemed to only decrease or totally eradicate the ejaculate, and this was the only difference found between the study groups. Furthermore, both laser and TURP treatments improved pain and/or discomfort. Generally, laser procedures do not seem to compromise sexual function more than standard TURP. There is a detailed discussion on specifically HoLEP by Montorsi et al. [10]. Also, erectile function, as measured with the erectile function domain of the International Index of Erectile Function (questions 1–5, 15) showed no reduction in the follow-up from baseline in either the HoLEP and TURP groups; as expected, there was a similar decrease in the ejaculatory domain in both groups. However, there is still no accurate sexual functional analysis for KTP laser treatments.

CONCLUSIONS

Among the surgical alternatives to TURP, laser techniques seem to be important for treating BPH and reducing overall perioperative morbidity. Whilst generally there are no long-term follow-up data for the newest approaches, increasing evidence seems to confirm the efficacy and reliability of the HoLEP technique. However, the steep learning curve and the initial costs seem to have limited the widespread adoption of the procedure. Interesting new data are available for KTP laser prostatectomy and it is progressively gaining attention as a possible option for TURP, offering encouraging preliminary results. However, long-term follow-up and accurate controlled comparative studies are mandatory to correctly assess the results and to help the urologist to select the appropriate surgical approach to each patient, offering the most cost-effective, reliable and durable treatment for BPH.

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Abbreviations: HLP, holmium laser prostatectomy; KTP, potassium-titanyl-phosphate (vaporization of the prostate); HoLAP, holmium laser vaporization of the prostate; HoLEP, holmium laser enucleation of the prostate; ILC, interstitial laser coagulation; OP, open prostatectomy.