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Comparison of UK and European Association of Urology (EAU) guidelines for kidney cancer management

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Abstract

Clinical practice frequently utilises guidelines on how specific conditions should be managed. For urologists in the UK a range of sources are used as guidelines for the management of kidney cancer. These include documents from national bodies such as the National Institute for Health and Care Excellence (NICE), professional bodies as well as those prepared by individual groups of clinicians within regional cancer networks. In this article the European Association of Urology (EAU) guidelines on renal cell carcinoma are compared to guidelines used in the UK for this disease. Broadly consistent variations exist related to regional practice patterns, funding and the currency of the various guidelines. A specific strength of the EAU guidelines is the regular updating of these allowing incorporation of new evidence. These however do not consider the funding model for healthcare of the UK which dictates the availability of some treatment modalities and thus in some areas are not applicable. Current guidelines for kidney cancer developed within the UK are inconsistent and often outdated in terms of evidence sources. Broader use of the EAU guidelines within the economic restrictions of healthcare in the UK may result in a more consistent practise utilising current evidence sources in the management of kidney cancer.

Keywords

British Association of Urological Surgeons, European Association of Urology (EAU), guidelines, kidney cancer, National Institute for Health and Care Excellence (NICE), UK

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Introduction

Clinical guidelines provide recommendations on how healthcare professionals should manage specific conditions. These can encompass all aspects of care including prevention, screening and diagnosis, treatment and longer-term care. Guidelines can be developed by specialist societies, national or regional healthcare bodies as well as individual institutions such as hospitals. Various international specialist societies have developed guidelines for the management of kidney cancer. These include the European Urological Association (EAU),[1] European Society of Medical Oncology (ESMO),[2] and the American Urological Association (AUA).[3,4] National healthcare bodies, which may comprise government-sponsored organisations such as the National Institutes of Health[5] or collaborative groups such as the National Comprehensive Cancer Network,[6] also generate guidelines.

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Table 1. Gradings of the evidence and recommendations in EAU kidney cancer guidelines.

(a) Level type of evidence (LE).

Level type of evidence		Number of conclusions
Ia	Evidence obtained from meta-analysis of randomised trials	3 (2%)
Ib	Evidence obtained from at least one randomised trial	28 (28%)
2a	Evidence obtained from one well-designed controlled study without randomisation	16 (11.5%)
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study	15 (11%)
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports	61 (44%)
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities	16 (11.5%)

(b) Grade nature of recommendations.

Grade nature of recommendations		Number of guideline recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial	17 (29%)
B	Based on well-conducted clinical studies, but without randomised clinical trials	12 (20%)
C	Made despite the absence of directly applicable clinical studies of good quality	30 (51%)

EAU guidelines

The EAU, which was founded in 1972, has as one of its key objectives the maintenance of urological standards across Europe. With this intention it regularly publishes guidelines on a range of topics to assist practicing urologists as one of its core educational activities.

The EAU guidelines on renal cell cancer were initially published in 2000. Regular updates have been issued – 2001 and 2002 (limited), 2006 (full update), 2007, 2008, 2009, 2010 and 2013 (limited). A further full update was published in 2014 followed by limited updates in 2015 and 2016. The current updated guidelines can be viewed and downloaded from the EAU website – http://uroweb.org/guideline/renal-cell-carcinoma/.

The authorship group and methodologies employed in distilling evidence and preparation of the EAU guidelines are detailed both within each version or update and more extensively elsewhere for the full update of 2014.[7] The evidence is based on systematic literature searches, the Cochrane Central Register of Controlled Trials and reference lists in publications and review articles. Early versions of EAU guidelines were largely based on traditional narrative reviews with conclusions and recommendations largely reflecting expert opinion. The Cochrane methodology in undertaking systematic reviews was adopted in 2011. Currently the majority of sections have been updated based use of systematic reviews including most aspects of surgery and systemic therapies. A few sections of the document remain as structured literature assessments including epidemiology, aetiology, pathology, staging and grading classifications and follow-up protocols.

Despite the changes in methodologies the publications available for use on renal cell carcinoma (RCC) are largely based on retrospective reviews from national and institutional data sets, uncontrolled studies and only a limited number of controlled trials, limiting the strength of many of its conclusions and recommendations. The guidelines indicate within each topic gradings of the level type of evidence (LE) and based on this the grade nature of the recommendations (GR) provided – a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). These are stratified as shown in Table 1. Consequently significant variability exists in the quality of evidence available. In total 46 of 198 (23%) conclusions and recommendations have no strong or evidential basis and are essentially derived from expert or considered opinion. These include all seven of the conclusions or recommendations for follow-up after ablative therapies and surgery for localised disease. Higher levels of evidence

base exist for first- and second-line systemic therapies – reflecting the availability of published results of industry-sponsored randomised controlled trials. In contrast, recommendations for second-line treatment of non-clear cell carcinoma and poor prognosis clear cell carcinoma as well as third-line treatments were essentially purely based on expert opinion. Intermediate levels of evidence (i.e. 2 and 3) and grades of recommendations (i.e. B) apply to guidelines on surgical treatments and management of localised disease.

United Kingdom (UK)

In the UK a range of guidelines have been developed in relation to kidney cancer. These have come from specialist professional societies, national bodies as well as regional cancer networks.

a. Two professional bodies – the British Association of Urological Surgeons (BAUS) and the British Uro-Oncology Group (BUG) – have jointly published a guideline on the management of kidney cancer.[8] The authorship group, methodologies employed to gather information or techniques of evidence evaluation are not described. These guidelines, published in 2012 without subsequent updating, were supported by an unrestricted educational grant from a pharmaceutical company. BAUS have now endorsed the EAU guidelines – recognising that within these there may be some aspects or recommendations not applicable to the UK.
b. In 2002 NICE published Guidance on cancer services: Improving outcomes in urological cancers.[9] This landmark publication included guidelines for kidney cancer covering treatment recommendations based on evidence available at the time. A substantial portion of this document was focussed on the delivery of care for patients with urological malignancies, including kidney cancer, which would appear to have been its principal purpose. Its impact was thus predominantly directed to the need (or perhaps requirement) for regional networks within the National Health Service (NHS), structured multidisciplinary care and patient pathways.
c. NICE have also provided a number of guidelines for kidney cancer related to specific interventions with a specific emphasis on new treatment modalities, particularly systemic agents for metastatic disease. To date seven have been published on interventional procedures and five on drug treatments. A further review planned in 2017 is to appraise the clinical and cost effectiveness of axitinib, everolimus, sorafenib and sunitinib for treated advanced or metastatic RCC in line with their respective marketing authorisations in the UK.

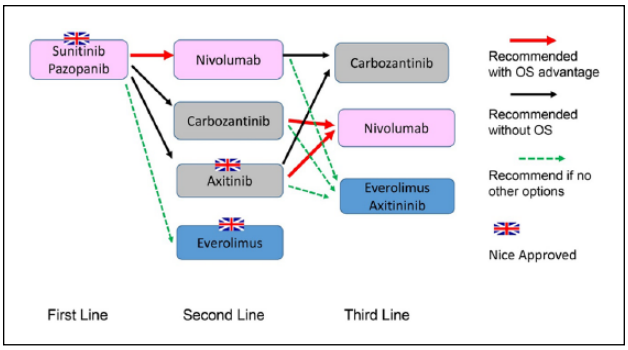

Figure 1. EAU Guidelines for treatment recommendations of metastatic clear cell renal cell carcinoma with NICE-approved treatments indicated.
EAU: European Association of Urology; NICE: National Institute for Health and Care Excellence; OS: overall survival.

d. Many regional urology cancer networks have also now developed guidelines for kidney cancer subsequent to the NICE publication – a number of which are accessible in the public domain. A total of 15 guidelines on kidney cancer were retrieved from the internet either as separate documents or embedded within larger guidelines covering urological cancer. These have largely been generated as supporting documents to operational policies around patient pathways of care and multidisciplinary teams (MDTs) managing patients with kidney cancer.

The format and content of the guidelines had considerable variation with all prepared by one or more local clinicians. The vast majority outlined the local pathways of care from the point of referral through to completion of treatment and follow-up.

The EAU guidelines are either heavily referenced or form the basis of many of these documents. In two the EAU guidelines were referenced without reproduction as the clinical guideline base and thus dealt with operational matters only. The EAU guidelines were reproduced in whole or part – with and without reference within several network guidelines. The remainder had clinical guidelines that were based on referenced literature reviews by the authors or unreferenced statements. Some of the referenced reviews included the EAU guidelines, in various iterations. What was termed ‘local practice’ was also acknowledged as the basis for some of the content.

Publication dates of the guidelines were 2005(1), 2010(1), 2011(2), 2012(2), 2014(5), 2015(3), 2016(1). Many of the publications indicated planned updates which were not able to be sourced from either the web or publicly accessible hospital or network websites from which the original guideline had been sourced. It is unknown whether these and other guidelines have been updated or published but they appear only on Trust or other intranet sites.

Table 2. EAU summary of drug treatment recommendations for systemic therapy in metastatic RCC.

RCC type	Risk group	First line	LE	Second line	LE	Third line	LE
Clear cell	All	**Sunitinib**[a] **Pazopanib**[a] *Bevucizamab(+IFN)*	1b	*Nivolumab* *Carbozantinib* **Axitinib**[a] **Sorafenib**[a] *Everolimus*	2a 2a 2a 2a	*Nivolumab* *Carbozantinib* *Everolimus*	2a 2a 2a
Clear cell	Poor	*Temsirolimus*	1b	Any targeted drug	4		
Non-clear cell	Any	**Sunitinib**[a] *Everolimus* *Temsirolimis*	2a 2b 2b	Any targeted drug	4		

EAU: European Association of Urology; RCC: renal cell carcinoma; LE: level of evidence; IFN: interferon. [a]Drugs approved for first- and second-line treatments by National Institute for Health and Care Excellence.

Comparison between EAU and UK guidelines

BAUS/BUG guidelines

The joint BAUS/BUG guideline essentially comprises a narrative review with conclusions and recommendations largely reflecting expert opinion. Neither the methodologies employed nor authorship are described. It would appear to comprise a structured literature search – which was the stated methodology used by EAU guidelines up to 2012 when the BAUS/BUG guideline was published. There appears to be no plan to revise this guideline, perhaps in part reflecting a resourcing issue as its publication was dependent on external funding. It does not appear to have provided a substantial resource as a reference document for preparation of network guidelines for kidney cancer in the UK. Thus unfortunately, whilst a well-referenced considered review, it no longer appears a useful guideline to underpin management of kidney cancer in the UK.

NICE

Guidance on cancer services: Improving outcomes in urological cancers[9] published by NICE provided some guidance on clinical management of kidney cancer. This is both brief and now outdated due to the changes in treatment options and practice which have occurred since its publication. With surgery, radical nephrectomy was stated as preferred treatment of the primary tumour with minimal consideration of nephron-sparing or minimally invasive approaches. Immunotherapy was also the only option for systemic disease. NHS England with the establishment of Clinical Reference Groups is in the process of updating aspects of the 2002 document and have provided in draft form service specifications for management of urological cancers. The purpose of this is to underpin commissioning of services. Consequently its content reflects organisational issues and service configurations without specific guidelines for treatment.

NICE has subsequently provided recommendations in two specific domains of care for kidney cancer – technology related, principally related to interventions for localised disease, and drug agents in metastatic disease.[10]

Drug treatment. At the present time NICE has recommended sunitinib and pazopanib as first-line agents in the treatment of metastatic kidney cancer. Axitinib, sorafenib and sunitinib are approved as second line therapies. These recommendations contrast with the broader spectrum of systemic therapies recommended in the EAU guidleines as illustrated in Figure 1. Also whilst NICE stipulates performance status, it does not stratify use based on histological sub-type or risk group as outlined in EAU guidelines(Table 2).

The fundamental difference in these recommendations reflects methodology as NICE evaluates both clinical efficacy as well as cost effectiveness. Pricing of drugs heavily influences the latter and a critical determinant in recommendations by NICE which effectively translates into funding by the NHS.

Technology. NICE has evaluated and approved five procedures for treatment of localised disease – laparoscopic nephrectomy, laparoscopic partial nephrectomy, cryotherapy (percutaneous and laparoscopic) and percutaneous radiofrequency ablation.[10] Its evaluation was underpinned by safety and efficacy without consideration of costs. Each procedure was considered in isolation without stratifying any recommendation as the preferred option for specific patient scenarios.

Cancer networks

The local guidelines detail either narratively and/or diagrammatically the pathways of care, decision-making

Table 3. Examples of recommendations that appear in local UK kidney cancer guidelines compared to current EAU guidelines.

Local guideline	EAU
Open radical nephrectomy is the treatment of choice for tumours >4 cm	Laparoscopic RN has lower morbidity than open surgery (1b), oncological outcomes for T1–T2a tumours are equivalent between laparoscopic and open RN(2a), laparoscopic nephrectomy is recommended in patients with T2 tumours and masses not treatable by PN (B)
Laparoscopic nephrectomy may be considered as an alternative to open radical surgery in suitable tumours, all tumours<5 cm as well as larger tumours where anatomy is suitable	PN achieves similar oncological outcomes to RN for clinically localised tumours, i.e. cT1 (1b), PN is recommended in patients with T1a tumours (A), PN should be favoured over RN in patients with T1b tumours (B)
Biopsy rarely alters therapeutic options and may be considered where (a)unusual radiological findings or(b) clinical or radiological suspicion of alternative diagnosis, e.g. lymphoma	Renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology (c), percutaneous biopsy is recommended in patients in whom active surveillance is pursued (c)
Post-RN – low-risk – no follow-up after six weeks	US at six months, two and four years, CT at one, three and five years (C)
Preoperative renal artery embolisation facilitates excision of large vein-invading tumours	Tumour embolisation or IVC filter does not appear to offer any benefits (C)
Cytotoxic chemotherapy may be considered for selected patients who have aggressive variants of RCC and have not responded to anti-VEGF therapy	In patients with clear cell mRCC chemotherapy is not considered effective (B)
Medroxyprogesterone acetate may be considered in patients unsuitable for anti-VEGF treatment	No comment

UK: United Kingdom; EAU: European Association of Urology; RN: radical nephrectomy; PN: partial nephrectomy; US: ultrasound; CT: computed tomography; IVC: inferior vena cava; RCC: renal cell carcinoma; VEGF: vascular endothelial growth factor; mRCC: metastatic renal cell carcinoma.

process related to multidisciplinary team composition and input as well as time lines for treatment completion which are not covered in EAU or other international guidelines.

Clearly a number of local guidelines reflect the EAU guidelines either entirely or substantially. The other local guidelines available are also broadly consistent with the EAU in terms of diagnosis, interventions for localised disease, surgery in locally advanced and metastatic disease as well as the indications and strategies for treatment of metastatic disease. With respect to the details of actual clinical care, there is variation in the network guidelines when these are compared to each other as well as the EAU guidelines. These variances however are not consistent across the UK and relate to the lack of currency of the available local guidelines as well as the methodology used in their generation.

In some areas where guidelines deviate from the EAU this appears heavily influenced by established practice patterns of local clinicians – with clear differences between networks. In some cases the network guidelines are rather opaque – exemplified by the content of one containing the unreferenced statement 'Clinical management of patients including follow-up should follow locally agreed clinical policies in line with NICE service guidance and clinical guidelines'. In others isolated areas of difference appear to reflect the opinion or established practice of one or a small number of individuals. Illustrative examples of this are shown in Table 3 which are compared to EAU guideline statements relevant to the local guideline.

With treatment of systemic disease variance in network guidelines is also present. This ranges from closely reflecting the EAU guidelines (including non-NICE-approved agents) to mentioning only generic terms for drugs such as targeted therapies or tyrosine kinase inhibitors. Both temsirolimus and everolimus were recommended in several guidelines with comments that regional cancer drug funds provided this for patients on application. It is uncertain whether actual practice reflects published network guidelines due to NICE constraints or whether there are true regional differences in practice consistent with the inter-regional variations in published guidelines.

A further variation noted between local guidelines relates to follow-up protocols. As stated in the EAU guidelines *'there is no evidence whether early versus later diagnosis of recurrence improves survival'* in kidney cancer. Consequently the conclusions and recommendations in this domain are reflective of opinion and of low evidence base with no consideration of cost effectiveness. UK guidelines are generally consistent with those outlined in the EAU

guidelines – with individual documents suggesting more and less intensive protocols with a strong emphasis on cross-sectional imaging and specialist clinic review. Given the economic burden that the current guidelines could represent on NHS resources, this area would appear worthy of consideration by NICE.

Discussion

EAU guidelines provide a robust methodology in synthesising what evidence there is in kidney cancer in providing treatment recommendations. They do not appear to have any clear bias (either pharmaceutical or industry) with a regular programme of review and update. The treatment guidelines do not incorporate economic considerations – a difficult exercise as these vary between healthcare systems with different funding sources and constraints.

Within the UK there are numerous regional guidelines for kidney cancer created for use or reference by cancer networks and centres. These largely clinician-authored guidelines currently accessible reflect closely, and usually heavily source these from those of the EAU. These have serious limitations as none appear to have robust methodology with weaknesses, including referencing of single papers. As a result these essentially comprise 'considered opinion' reviews by local experts. Local guidelines are generally out of date with no inbuilt programme of review/revision as evidence evolves. The preparation of these is likely to have consumed a considerable amount of clinician time with limited resources to match what the EAU can provide. Consequently maintenance of currency appears a concern that needs to be addressed.

NICE guidelines have good methodology including cost effectiveness in deriving conclusions. In contrast to other guideline sources NICE also engages industry representatives in its consideration of evidence in developing recommendations. It also restricts recommendations to specific topics, usually new drugs or technology, without providing any overarching guidelines on kidney cancer management. Local guidelines incorporate patient treatment paths and clinical decision-making processes (e.g. MDTs) – which are highly relevant to how we practise. The EAU guidelines do not provide either practice frameworks or cost evaluations – both of which are important considerations, locally and nationally, in the UK with its NHS model of care.

An important requirement for clinical guidelines is that these remain current and evidence based. Drug development in kidney cancer is extremely dynamic with a number of new agents, including immunotherapies, currently undergoing trial evaluation. Technological changes also appear likely to evolve and may change practice options in minimally invasive procedures – with the evidence base for their use emerging or strengthening. Changes in these two areas are thus likely to underpin practice changes in kidney cancer. As these are also potentially expensive, adoption within the financially constrained environment of the NHS will require careful evaluation of true cost/benefit. Thus NICE evaluations will need to continue to influence clinical guidelines which will at times conflict with the EAU guidelines. Whilst the latter will continue to provide these within a hopefully increasing evidence base framework, these are unlikely to consider economic constraint as a consideration.

Conclusions

EAU guidelines provide a useful evidence base of information on how to treat kidney cancer. It is regularly updated and has scientific merit relevant to the UK. In the UK NICE will inevitably dictate practice – on economic grounds and thus their evaluations will restrict UK guidelines even in the context that an intervention may be effective/evidence based but unsustainable within our budget. This will particularly influence drug treatment and minimally invasive technologies.

Local guidelines should avoid attempts to generate independent evidence-based documents varying in both their quality and conclusions. Rather these should focus on local organisational and operational delivery of care based upon nationally consistent guidelines. It would appear most practical that these are an amalgam of the most current versions of the EAU and NICE guidelines.

Conflicting interests

The author declares that there is no conflict of interest.

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Ethical approval

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Informed consent

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