

Scientific & Policy Briefing on

KIDNEY CANCER

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1. Foreword

Although kidney cancer is a relatively rare cancer, it is the most lethal of the genitourinary cancers. As the population ages and the prevalence of known risk factors such as obesity (excess body weight) and hypertension (high blood pressure) increases, we predict a growing burden of kidney cancer. The International Agency for Research on Cancer (IARC) projects a 22% increase worldwide by 2020¹.

Kidney cancer is of particular significance within Europe as it has among the highest incidence in the world, particularly in Eastern Europe². In 2012, the Czech Republic showed the highest incidence rates (34.9/100 000 in men and 15.0/100 000 in women)³. The incidence rates have been slightly increasing over time in some European countries and have remained stable in others.

The mortality rates have been slightly decreasing over time, particularly in Western and Northern Europe. The rising incidence and the slight decrease in mortality trends of kidney cancer may be partly explained by the increased use of diagnostic imaging, which can result in incidental findings of small renal masses^{2,4}.

Significant differences in the incidence of kidney cancer in European countries underscore the importance of primary prevention, early detection and effective treatment to ensure an increased quality of life. European action is urgently required to reduce the burden of kidney cancer on patients and society and to ensure equal access to diagnostic tools and innovative treatments across different European countries and regions.

The principal requirement is a greater recognition of kidney cancer as a European healthcare problem. Improvements in kid-

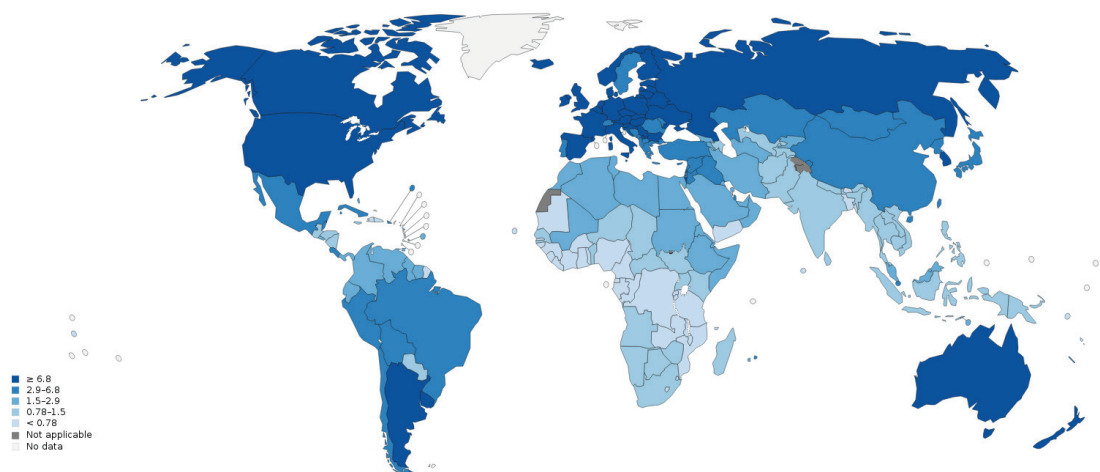
ney cancer care depend primarily on closer collaboration and knowledge sharing between EU Member States and across the healthcare sector. The collaboration should include caregivers and researchers, the industry, professional societies such as the European Association of Urology (EAU) and European Society for Medical Oncology (ESMO) and patient organisations.

Most patients with advanced or metastasised kidney cancer in the EU have access to the drug sunitinib in the first line, but access to potentially curative treatments (surgery and immune-oncology) is limited. Consistency in patient access to these treatments is hindered by national rules on licencing and treatment guidelines authorisation, pricing, reimbursement and prescription.

The EU supports research focused on the causes and mechanisms of cancer, translation of basic knowledge into clinical applications and clinical research for new or improved medical interventions. The European Commission reported that from 2007 to 2013, a total of about 1,000 projects on cancer were funded with 1.5 billion euros. Since 2002, only 21 projects dedicated to kidney cancer have been funded, which demonstrates a disproportional underrepresentation of allocated funds to renal cancers (http://cordis.europe.eu/home_en.html). Increased EU funding of research, wider recognition of kidney cancer as a European health burden, and elimination of inequalities in care between Member States are needed to ensure that all patients with kidney cancer have timely access to affordable innovative treatments.

This scientific and policy briefing provides general information and the latest scientific evidence on kidney cancer and highlights the key challenges in improving patient outcomes.

Estimated age-standardized rates (World) of incident cases, both sexes, kidney cancer, worldwide in 2012



2. Introduction

Kidney cancer is the 7th most commonly diagnosed cancer with approximately 115,200 new cases and 49,000 deaths in Europe recorded each year³.

The most common type of kidney cancer in adults is renal cell carcinoma (RCC) which represents over 90% of all renal malignancies. Other types of kidney cancer include transitional cell cancers, Wilms tumours and renal sarcomas. RCC occurs roughly twice as often in males as in females. The incidence rates are highest among people older than 75 years, but more young adults are also being diagnosed with kidney cancer. Wilms tumour, the most common type in children, and some other paediatric kidney tumours have a better prognosis than adult tumours. Clear cell sarcoma of the kidney in children has a poor prognosis.

RCC is generally asymptomatic in early stages, which means that there are no clear symptoms to indicate its presence. If RCC does cause symptoms it is usually a sign that the disease is already at an advanced stage. The symptoms of advanced RCC include: blood in the urine (haematuria), lower back pain on one side, a mass on the side or lower back, fatigue, anaemia (low red blood cell counts), weight loss, and fever not caused by an infection and that does not go away. Other findings secondary to a renal tumour are a non-reducing varicocele (enlarged veins in the scrotal sac), and polycythemia (elevated red blood cell counts). These symptoms can also be caused by other diseases. If these symptoms occur, seeing a doctor is warranted.

Increased use of imaging techniques in Western countries, such as ultrasound and CT scans, has increased the detection of early stage disease. This increase of imaging data has naturally led to treatment of small renal masses without the evidence that supports the necessity of such treatments. In particular, whether older patients (with potential co-morbidities) actually benefit from intervention at this stage of disease remains unclear. Evidence for the management of small renal masses is of low quality, and intervention in the case of asymptomatic isolated small renal masses may be unnecessary. Strategies to prevent over-treatment with unnecessary morbidity for the patients and costs for the society are needed.

In Europe, overall mortality rates have stabilised or decreased since the early 1990s⁵. Apart from a role of reduced tobacco smoking in men, the cause of these mortality trends remains undefined. In some European countries (Ireland, Croatia, Greece, Portugal and Slovenia), mortality rates still show an upward trend.

The explanation for international variations in incidence and mortality of kidney cancer is probably a combination of genetic variations unique to ethnic and regional populations and lifestyle/environmental factors coupled with availability of healthcare resources for imaging, variations in early detection and treatment of tumours at lower stage (smaller tumours), variable treatment options, skilled healthcare professionals and inaccurate RCC data in countries where investment is needed in cancer reporting⁴.

Kidney cancer imposes a significant burden on patients, families and healthcare systems.

Health-related quality of life (HRQOL) deteriorates with increasing tumour burden and burden of metastases (spread of cancer cells to another part of the body) along with the impact of treatment-related side effects. The financial/economic burden on healthcare systems is expected to increase dramatically throughout Europe over the coming years because of the high cost of diagnosis and treatment that often involves surgery, hospitalisation and regular follow-up. At least 20% of people with RCC have metastatic disease (mRCC) at first diagnosis. Up to 30% of people undergoing potentially curative surgery develop metastases during follow-up⁶. The cost for treatment of advanced/mRCC patients is high because of the very high cost of targeted drugs, especially beyond first line and the cost of management of side effects⁷⁻⁹. It is expected that costs will further increase with the introduction of immune checkpoint inhibitors into the treatment paradigm. Approximately 85% of RCC patients with bone metastases experience skeletal-related events which results in an increase in costs associated with hospital visits¹⁰.

The EU must raise greater awareness of kidney cancer, highlighting the risk factors, symptoms, importance of early diagnosis, treatment options, quality of life issues and social consequences. Additional investments in clinical research and new technologies for improving diagnostic and therapeutic accuracy should be encouraged. This should lead to individualised risk assessment and the development of new treatments, which could result in better management of kidney cancer in Europe.

3. Risk factors and prevention

3.1 ESTABLISHED RISK FACTORS

Despite the increasing incidence of kidney cancer, the causes are poorly understood. As with most cancers, it is commonly a combination of risk factors and ageing. The risk of developing RCC increases with age. The average age at the time of diagnosis of RCC is 64 years.

Three most established modifiable risk factors for RCC with increasing prevalence in the general population:



Cigarette smoking



Excess body weight (obesity)



High blood pressure (hypertension)

Kidney disease and long-term dialysis are also significant risk factors for RCC as the rates are likely to further rise with the increasing life expectancy.

Inherited genetic predisposition is thought to be an underestimated risk factor.

- *Cigarette smoking*: increases the risk of RCC by 54% in male and 22% in female former and current smokers¹¹.
- *Obesity (body mass index ≥ 30 kg/m²)*: 5 kg/m² higher BMI is associated with a 25% higher risk of kidney cancer¹².
- *Hypertension*: uncontrolled elevated systolic (≥ 160 mm Hg) and diastolic (≥ 100 mm Hg) blood pressure is associated with a two- or threefold increased risk of RCC¹³.
- *Kidney disease and long-term dialysis*: increases the risk of RCC¹⁴.
- *Inherited genetic predisposition*: Hereditary kidney cancer is found in 5 to 8% of all kidney cancer cases and genetic screening is recommended for all RCC patients 46 years old or younger¹⁵. However, this contribution of hereditary RCC may be significantly underestimated. Having a first-degree relative with RCC is associated with a two to fourfold increased risk of RCC¹⁶. Because hereditary RCC syndromes may also have characteristic extrarenal manifestations, diagnosis may not always be based on a family history of RCC; for example, a first-degree relative of an RCC patient with a brain hemangioblastoma is highly relevant for early detection of RCC in family members.

3.2 RISK FACTORS WITH CONFLICTING OR LIMITED EVIDENCE

A number of other factors are associated with higher risk of RCC but data from the literature are still inconclusive.

- *Kidney stones*: there is a significant increased risk of RCC in males with prior kidney stones¹⁷.
- *Viral hepatitis C infection*¹⁸.
- *Occupational carcinogenic exposures*: although the prevalence of occupational carcinogenic exposures (petroleum products, asbestos, heavy metals, arsenic in drinking water) has been reported to be high in low- and middle-income countries, the effects have not been studied¹⁹.
- *Pain killers*: a recent meta-analysis (combining data from multiple studies) demonstrated that acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of developing kidney cancer²⁰.
- *Meat intake and intake of related mutagens (agents that cause genetic mutations)* are suspected risk factors²¹. Recent data support an association between red and processed meat consumption and risk of RCC only in women²².
- *Sodium intake*: sodium intake increases the RCC risk, particularly if fluid consumption is low, whereas fluid and potassium intake was not found to increase the RCC risk²³.

3.3 PREVENTION

It has been estimated that up to half of the overall burden of all cancers can be prevented. The European Code against Cancer sets 12 recommendations that European citizens can apply to help to reduce their cancer risk by avoiding or reducing carcinogenic exposures, adopting a healthy lifestyle, or participating in vaccination programmes or organised screening programmes for bowel cancer, breast cancer and cervical cancer (<https://cancer-code-europe.iarc.fr>). The fourth edition of the Code has been developed by European cancer experts, scientists and other experts from across the EU and is based on the latest scientific evidence available^{24,25}.

Avoiding smoking and maintaining normal blood pressure and normal weight can reduce the risk of developing kidney cancer.

REDUCE SMOKING

The new Tobacco Products Directive (https://ec.europa.eu/health/sites/health/files/tobacco/docs/dir_201440_en.pdf) which became EU law on 20 May 2016 contains new rules on how tobacco products and related products should be labelled, packaged and manufactured. The Directive aims to decrease the consumption of tobacco in Europe and to make tobacco products less attractive to younger people. The EU and its Member States have taken various measures to reduce tobacco consumption in the form of legislation, recommendations and anti-smoking campaigns and should continue their activities as the prevalence of smokers in the EU is still high. There is no decrease in overall smoking rate in the EU (26%) since the most recent survey from 2014. Amongst young Europeans aged 15 to 24 the rate has increased from 25% in 2014 to 29% in 2017 (http://data.europa.eu/euodp/en/data/dataset/S2146_87_1_458_ENG).

REDUCE HYPERTENSION

In 2013, the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) has developed guidelines for the management of high blood pressure and provides recommendations for home and ambulatory blood pressure monitoring. The ESH developed an ESH care app for smartphones and tablets (<http://www.eshonline.org/guidelines/blood-pressure-monitoring/>). A global effort of policy makers is needed to im-

prove identification and treatment of high blood pressure within the European population.

REDUCE OBESITY

In 2007, the European Commission published a white paper on a strategy on nutrition, overweight and obesity-related health issues (https://ec.europa.eu/health/nutrition_physical_activity/policy/strategy_en) in order to encourage an integrated EU approach to contribute to reducing ill health due to poor nutrition, overweight and obesity. The European Association for the Study of Obesity (EASO) organised this year a summer school to train trainers in the prevention and management of obesity. Obesity has become a worldwide epidemic and its prevalence has been projected to grow by 40% in the next decade. These findings underpin the need for more effort to abate the rising trends in obesity as it has implications for the risk of diabetes, hypertension and chronic kidney disease and has been shown to be an important risk factor for kidney cancer.

A balanced diet high in fruits, whole grains and vegetables and low in fat with regular exercise are recommended because they are beneficial for overall health. It is advisable for all RCC patients or for those individuals at risk to exercise and maintain a healthy weight.

4. Diagnosis and prognosis

4.1 DIAGNOSTIC TOOLS

SCREENING

Currently, there is no standard routine screening test recommended for kidney cancer. Screening programmes are most efficient and cost-effective if they target high-risk populations. Identification of a high-risk population may allow a pilot study to determine whether a screening programme could affect survival in RCC²⁶. Aquaporin-1 and perilipin-2 hold promise as diagnostic and screening urinary biomarkers for clear cell or papillary RCC and in the differential diagnosis of imaged small renal masses²⁷. Cancer cells also have been found to secrete more exosomes than normal cells. These cancer exosomes have a potential role as urinary prognostic biomarkers²⁸. Currently, screening is only advised for patients with hereditary conditions, patients on long-term renal replacement therapy (either dialysis or transplant) who all have a higher risk of RCC. The development of new technologies for cancer screening, improvement in the selection of candidates for cancer screening and better understanding of the biological basis of carcinogenesis (development of cancerous cells) will allow for improvements in cancer screening over time²⁹.

Laboratory tests: Blood tests can detect some atypical findings associated with kidney cancer, such as anaemia and liver-test disturbances. A urine test can detect blood in the urine which is a common sign of more advanced kidney cancer.

IMAGING

Imaging is an important tool in the diagnosis of kidney cancer. The majority of the renal masses are detected incidentally by abdominal ultrasound (US) or computed tomography (CT) performed for unrelated symptoms or other medical reasons. CT remains the primary choice for radiological imaging. Magnetic resonance imaging (MRI) is an important alternative in patients requiring further imaging and in cases of contrast allergy, pregnancy, or surveillance. MRI may aid the identification of the tumour type and staging. Because of concern over radiation exposure, there has been a trend toward the higher use of MRI³⁰.

Chest CT and bone scans can be used to help determine if the cancer has spread (metastasised) to other parts of the body.

4.2 HOW ARE KIDNEY CANCER TUMOURS CLASSIFIED?

RCC comprise a broad spectrum of histological entities redefined in the 2016 World Health Organization (WHO) classification of the urinary system and male genital organs³¹. The three most common RCC types with genetic and histological differences are clear cell RCC (approx. 75%), papillary RCC (type I and II) (approx. 10%) and chromophobe RCC (approx. 5%). The remaining 5-10% include unclassified tumours and rare entities such as collecting duct carcinoma (CDC), renal medullary carcinoma and translocation RCC^{32,33}. Recently, even more new subtypes of RCC have been described³¹. RCC can be characterised by the presence or absence of a sarcomatoid component. Patients with RCC with sarcomatoid features, collecting duct carcinoma, renal medullary carcinoma and chromosome Xp11.2 translocation RCC have an aggressive clinical course and poor prognosis.

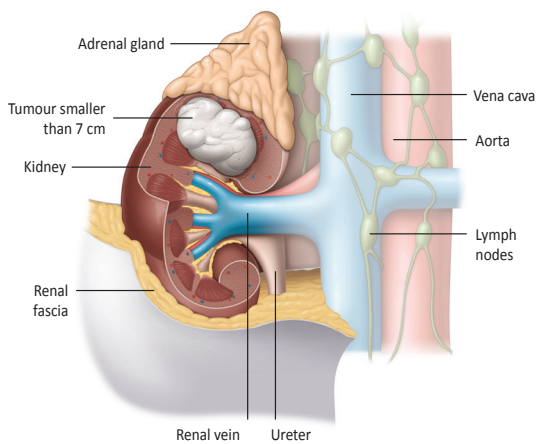
Kidney tumours are classified according to the stage, the subtype and aggressiveness of the tumour. The tumour tissue taken during biopsy or surgery is analysed. The pathologist determines the subtype of the tumour and whether or not it is an aggressive form. The tumour stage is based on the TNM classification. It describes how large, invasive and advanced the tumour is (T stage) and whether or not the cancer has spread to the lymph nodes (N stage) or other parts of the body (M; metastases).

The Fuhrman nuclear grade and the new WHO/International Society of Urological Pathology (ISUP) grade provide a rating that helps predict the aggressiveness of the cancer cells and ranges from grade 1 to 4³¹. A higher grade indicates a more aggressive tumour with a worse prognosis.

Hereditary kidney cancer accounts for 5-8% of kidney cancers³⁴. While some hereditary kidney tumours can develop with certain syndromes (of which von Hippel-Lindau is the most common), others have a genetic background which is poorly understood. Other inherited renal cancers are hereditary papillary RCC, hereditary leiomyomatosis and RCC, and Birt-Hogg-Dubé syndrome. These tumours show an earlier age of onset and the lesions can be multifocal, bilateral and heterogeneous³⁵.

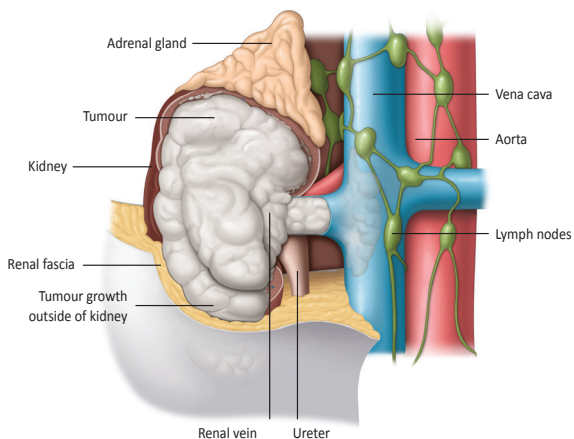
The following terms are used to indicate how advanced the kidney cancer is:

Localised: the cancer is limited to the kidney and has not spread. It may be a stage T1 or T2 tumour, depending on the size (up to 7 cm or more than 7 cm).



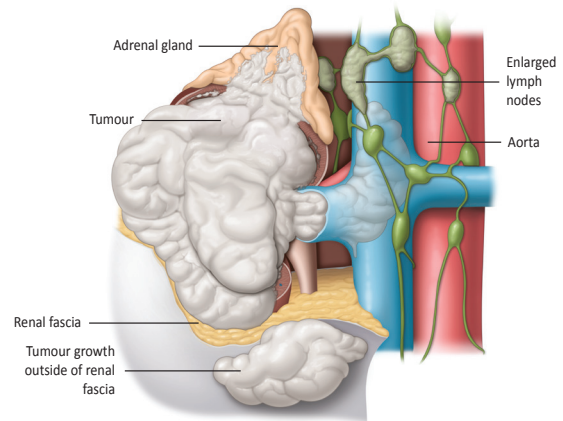
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Locally-advanced: the cancer has grown out of the kidney into the surrounding tissue and invaded veins, the adrenal gland and lymph nodes. It may be a stage T3 or T4 tumour depending on where and how far outside the kidney it has grown.



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Metastatic: the cancer has spread either to distant lymph nodes or other organs such as the lungs, or less frequently bones or brain. Metastatic disease can rarely be cured. Instead, the treatment will try to slow the growth of the tumour and the metastases.



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4.3 ASSESSING THE RISK OF A GIVEN KIDNEY CANCER

Prognostic factors for RCC include the primary tumour stage and size, the histological variant and the tumour grade, presence or absence of vascular invasion, lymph node invasion and distant metastases (number and localisation).

The classification of these RCC prognostic factors combined with age, family history and general health status are used to stratify the RCC patients according to their risk. This allows clinicians to develop a treatment plan and to determine a patient's prognosis. Several prognostic systems that combine prognostic factors have been developed and validated but none of these relied on molecular biomarkers. For clear cell RCC, potential prognostic biomarkers have been identified³⁶⁻³⁸. However, there are still no biomarkers for routine clinical use. Validation and integration of existing promising serum/urine RCC biomarkers into clinical care must become a priority.

The 3 main subtypes of RCC – clear cell, papillary and chromophobe - can occasionally be differentiated non-invasively on imaging based on characteristic radiologic appearances. Much greater research is also urgently required into the other, less common subtypes of RCC to define the biology of these tumours, clinical outcomes and potential treatments.

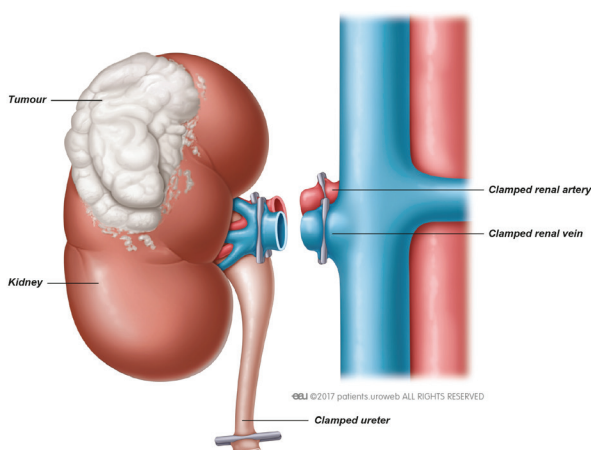
5. Treatment

The most important factors for selecting treatment are the stage, the subtype and the aggressiveness of the disease. The various RCC subtypes have different clinical courses and responses to therapy. Other factors are individual life expectancy, general health status and the preference of the individual patient. Individual recommendations may depend on the country and the healthcare system. The final treatment decision should be the result of shared decision-making between the person with kidney cancer and the healthcare team.

5.1 LOCALISED RENAL MASSES

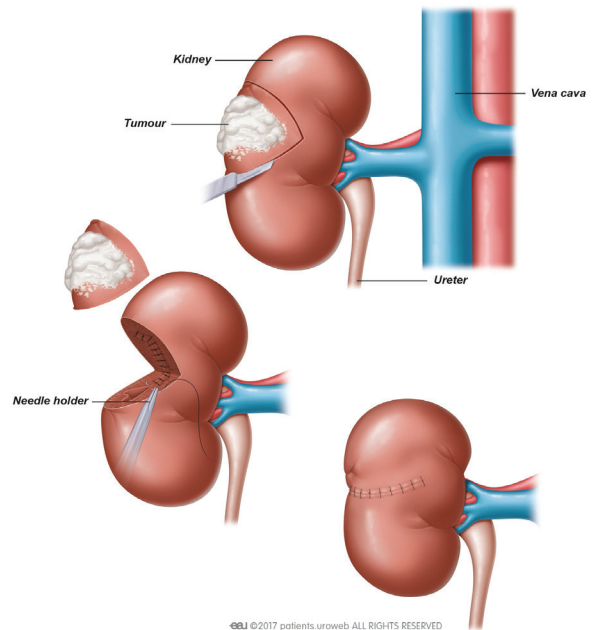
Several options exist for the treatment of small renal masses or clinically localised renal masses suspicious for RCC including active surveillance, thermal ablation and surgery (partial or radical nephrectomy). Surgery remains the corner stone of kidney cancer treatment and can be performed by an open or minimally invasive approach (laparoscopy and robot-assisted laparoscopy). If kidney cancer is treated by surgery early enough, the prognosis is mostly good. Complications after surgery are associated with age and comorbidity status. Each procedure has its own advantages and disadvantages and cost comparisons are highly variable in different healthcare systems.

Radical nephrectomy (RN): a surgical treatment in which the entire kidney is removed. RN has been the mainstay treatment for RCC for over 50 years.

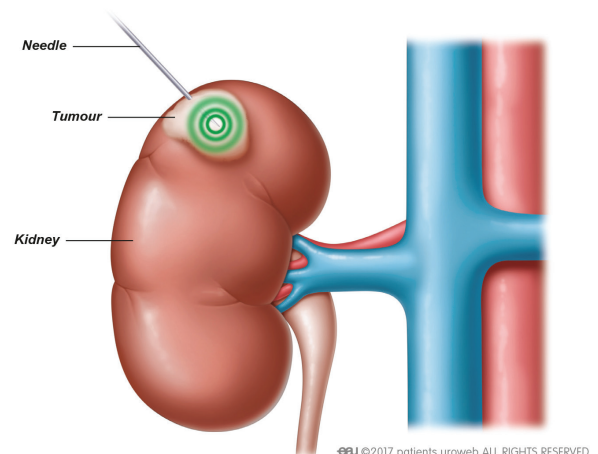


Partial nephrectomy (PN): a surgical treatment in which only the tumour is removed, and healthy kidney tissue remains intact (nephron-sparing surgery). Within the past decades there has been a shift towards increased use of PN. According to the EAU guidelines, PN is now considered the treatment of choice for pa-

tients with T1 tumours since it better preserves kidney function than RN. It is generally accepted that in patients with a normal contralateral kidney, PN is preferably when this is oncological and technically considered to be safe³⁹.



Thermal ablation: a treatment which destroys the tumour cells by freezing (cryoablation), or by heating (radiofrequency ablation; RFA or microwave ablation; MWA) and that is usually performed with a needle placed through the skin with image guidance. The indications remain limited to small renal masses in patients who are frail or older or poor surgical candidates. Ablation is not used or available in many countries.



Active surveillance: a way of not immediately treating a recently detected localised kidney cancer, but monitoring the tumour by regular visits. If the tumour is growing fast further treatment is planned. Active surveillance has emerged as an option for older and/or comorbid patients with small renal masses which have a low likelihood of aggressive malignancy and a limited life expectancy. However, active surveillance adoption is low, the more since minimal invasive techniques like thermal ablation became available.

Radical treatments require substantial follow-up if dialysis is needed. On the other hand, non-radical treatments also require additional resources for regular follow-up clinical appointments and the availability of suitable imaging and biopsy modalities.

5.2 LOCALLY ADVANCED RCC

Open RN is the standard of care when the tumour is expected to be completely resectable. Systematic removal of enlarged lymph nodes or the adrenal gland is advocated but their impact on survival remains controversial.

5.3 ADVANCED/METASTATIC RCC

Patients with mRCC are offered medical and surgical (cytoreductive nephrectomy/metastasectomy) combined therapies to prolong survival. To date, surgery remains a key component in the management of mRCC patients.

Nephrectomy: the role and timing of nephrectomy in combination with targeted therapy is still unclear^{40,41} and recent study results remain exploratory⁴². For most mRCC patients, nephrectomy is palliative and systemic therapy is necessary.

Local therapy for metastases of mRCC:

- Surgical resection of metastatic sites (metastasectomy) prolonged survival in mRCC patients with a favourable risk profile and metastatic sites amenable to complete resection. At present, complete metastasectomy before systemic therapy remains the primary treatment option⁴³.
- Radiotherapy for clinically relevant bone or brain metastases from RCC can be considered for significant relief from local symptoms (e.g. pain).

Systemic therapy: surgery is generally combined with drug therapy which can relieve the symptoms and may shrink the primary tumour and metastases. However, there is disparity in availability and familiarity with systemic therapy, with still few survivors even in rich countries.

- *Immunotherapy: Interferon-alpha and interleukin-2:* have been superseded by targeted therapy in the last 10 years.

- *Targeted therapy:* several angiogenesis inhibitors, which target the growth of the new blood vessels that tumours need to grow, are approved for RCC in Europe including sunitinib, axitinib, pazopanib, sorafenib, bevacizumab in combination with interferon alpha, temsirolimus and everolimus. They show improved survival rates and a better safety profile. Median overall survival in mRCC patients in clinical trials has increased beyond 2 years⁴⁴. However, complete and durable responses are rare and drug resistance will ultimately always develop. Cabozantinib is recently approved for second-line therapy with improved overall survival and response rate over everolimus⁴⁵.
- *Immune checkpoint inhibitors:* enhance the anticancer immune response by the patients' own immune system. Nivolumab which target the immune checkpoint protein PD-1 is recently approved for second-line therapy with improved overall survival, response rate and health related quality of life over everolimus^{46,47}.

Clear cell RCC-approved targeted agents tend to be significantly less effective for non-clear mRCC⁴⁸ and optimal treatment has yet to be determined.

In patients with RCC and bone metastases, bisphosphonates and denosumab are used as adjunct to systemic targeted therapies to prevent skeletal-related events⁴⁹. However, attention to bone health is variable in the different countries.

6. Living with kidney cancer

As the number of kidney cancer survivors continues to grow, patients, general practitioners, caregivers and the broader public should be better informed about the needs of kidney cancer survivors in order to improve their quality of life.

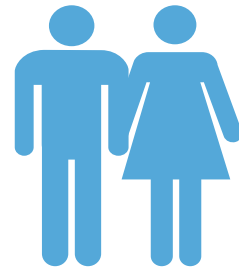
Health-related quality of life (HRQOL) issues associated with tumour burden such as anorexia, fatigue, pain, anaemia, hypercalcaemia (elevated calcium levels in the blood), venous thromboembolism (combination of a deep vein thrombus (blood clot) and pulmonary embolism (blockage in a lung artery by blood clots that travel through the bloodstream)) and psychological concerns along with the impact of treatment-related side effects require further study.

Undergoing treatment for kidney cancer is intense and will affect everyday life, work and social life. Patients need to obtain balanced and fair information on the advantages as well as the adverse side-effects of their management plans. After surgery or other treatment, they will probably feel tired or sick and may need help to resume normal everyday activities.

Follow-up is important to check general health, to manage any side effects from treatment, to watch for a return of the kidney cancer (tumour recurrence), and to watch for other types of cancers. The follow up after nephrectomy needs to be personalised/standardised according to the risk of recurrence (Leibovich prognosis score). The experience of a Dutch Cancer Institute has shown that a standardised follow-up alternatively done by the urologist and the nurse practitioner is feasible and efficient. It saves consultation time for the urologist and reduces financial cost due to fewer CT scans (https://issuu.com/uroweb/docs/european-urology-today-aug-sept_201/35).

It is important for patients to maintain or adopt a healthy lifestyle during and after treatment, including a healthy diet and regular physical activity. Nutritional deficiency is associated with higher mortality in people undergoing surgery for RCC. It is important that the person's nutritional status is assessed before surgery, and any potential need for nutritional supplementation is reviewed by the healthcare team⁵⁰.

People diagnosed with kidney cancer may be anxious about their prognosis. Oncology nurses play an important role in supporting patients with kidney cancer. They often serve as the patient's first line of communication (primary contact person) and help coordinate the many aspects of care throughout all the phases of the treatment (care coordination) and during the follow up (survivorship). Psychologists play an important role in providing psychological support of the patient and his/her family.



Treatment of kidney cancer can impact negatively on physical and psychosocial functioning. Survivorship information and assessment of supportive care needs for patients with kidney cancer and their families are crucial. Involvement and better integration of primary care in cancer management is essential to meet the demand of 40% increase in cancer incidence (Report from the ECCO 2017 Primary Care Track).

A shortage of kidney function (renal failure) may be a short-term or long-term side effect of treatments for kidney cancer. People can live a normal and healthy life with one kidney or even with only a part of one kidney. However, if the remnant kidney does not function properly, dialysis is needed to remove the wastes and extra water from the blood. Dialysis can be done in 2 ways. The patient will be connected 3 times a week to a dialysis machine in a dialysis centre (haemodialysis). Each session takes up to 6 hours. Peritoneal dialysis uses the patient's membrane that surrounds the organs in the abdominal cavity (peritoneum) and can be done at home. Patients who have both kidneys removed need to be on dialysis for the rest of their lives. Some patients can become candidate for a kidney transplant from a living donor (often a relative, spouse or friend) or from a deceased patient, after a given period of time without cancer recurrence.

PATIENT ORGANISATIONS

The role of patient organisations is pivotal to provide support and more detailed awareness on the specific need of people affected by kidney cancer on rehabilitation, late effects related to treatment, and returning to work after the acute treatment phase. Patient organisations are also working to address the survivors' needs by providing evidenced-based information such as the EAU Patient Information on kidney cancer, designing decision aid tools for the care of kidney cancer, and to develop rehabilitation/survivorship plans to reduce side-effects and problems (e.g. <http://www.esmo.org/content/download/124130/2352601/file/ESMO-Patient-Guide-on-Immunotherapy-Side-Effects.pdf>). All the steps of proper follow-up should be included into a personalised kidney cancer survivorship plan, to ensure that each individual has all the necessary information and retains full control over his/her life after the acute treatment. The ESMO-ECPC Survivorship Guide (2017) contains a checklist that people with kidney cancer can use in collaboration with their healthcare team in order to facilitate the return to a normal life (<https://www.esmo.org/content/download/117593/2061518/file/ESMO-Patient-Guide-Survivorship.pdf>).

The International Kidney Cancer Coalition (IKCC) is the global collaboration of kidney cancer patient organisations representing the kidney cancer community through advocacy, awareness, information and research. The IKCC website features an 'Information Hub' containing shareable information, graphics and materials about kidney cancer for patient organisations around the world. The website also features a searchable database of global kidney cancer clinical trials and a shared decision making booklet for people with advanced renal cell carcinoma to help patients in partnership with their healthcare team.

Patient organisations can also help patients with practical matters such as financial advice in relation to the socio-economic difficulties faced by many cancer survivors.

7. Future research

TREATMENT OF ADVANCED NON-CLEAR CELL RCC

Non-clear cell RCC subtypes represent 20-25% of all RCCs. They are also termed rare kidney cancers⁵¹. Like clear cell RCCs, these entities may be hereditary or sporadic. It is a heterogeneous group of diseases with distinct molecular drivers, histologies and clinical outcomes. Limited data are available for evidence-based treatment of non-clear cell RCC subtypes because of their low incidence and heterogeneity. The EAU RCC guideline panel recommends sunitinib over everolimus and temsirolimus for metastatic non-clear cell RCCs in first-line treatment, based on a recently performed systematic review⁵². However, there is a lack of strong evidence. The optimal treatment for patients with advanced non-clear cell RCC remains unclear⁵²⁻⁵⁵. Further well-coordinated multi-centre studies, subtype-specific analyses and translational research efforts are urgently needed to generate sufficient data to develop evidence-based recommendations for guidelines⁵¹.

GENE MUTATIONS

New research on the effect of gene mutations linked to kidney cancer may lead to the development of new drugs which target those abnormal pathways (personalised medicine)⁵⁶.

BIOMARKERS

Targeted therapies for mRCC are toxic and still expensive. Given the high cost of these emerging drugs mainly due to the high drug cost and the cost for management of treatment-related side effects, the development of effective biomarkers that can predict treatment response and drug toxicity is urgently needed⁵⁷.

Further research is needed to identify and validate biomarkers that may be used for the detection of kidney cancer.

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors that help the body to restore the immune system and recognise and attack cancer cells need to be further explored and hold more than promise. These agents are, for example, nivolumab, pembrolizumab and atezolizumab which target the immune checkpoint protein PD-1/PDL1 and ipilimumab which targets the checkpoint protein CTLA-4. Various immune checkpoint inhibitors are currently being investigated for use as a first-line agent in patients with mRCC. Future goals are to investigate the effect of novel immune-oncology strategies (immune checkpoint inhibitors and immune modulators, cancer vaccines, adoptive cell therapy, monoclonal antibodies, and cytokines)⁵⁸⁻⁶⁰.

combined with different established treatment modalities. Several trials evaluating the use of combination therapies with other immune checkpoint inhibitors and with anti-vascular endothelial growth factor (anti-VEGF) inhibitors are ongoing. The choice of drugs and the optimal administration sequence have yet to be determined. Immune biomarkers are needed to avoid ineffective treatment. Clinical trials evaluating various kidney cancer vaccines have been conducted, although none have demonstrated an improvement in survival so far⁶⁰.

NEOADJUVANT AND ADJUVANT TREATMENT

Additional medical treatment before surgery to shrink the tumour (neoadjuvant) or after surgery to maximise its effectiveness (adjuvant) in patients with locally advanced RCC should be further investigated. The updated EAU guidelines do not yet recommend adjuvant therapy with sunitinib for patients with high-risk RCC after nephrectomy⁶¹. The role of immune checkpoint inhibitors is currently being investigated in the adjuvant non-metastatic setting in 4 well-designed trials⁶⁰.

ROLE OF SURGERY IN MANAGEMENT OF MRCC

With the improvements of targeted therapies, the role of surgery in the management of mRCC requires reassessment. Results of ongoing prospective trials regarding the role and timing of cytoreductive nephrectomy in mRCC patients are pending. Further studies are required to determine patient selection and the optimal timing of metastasectomy. The actual timing of targeted therapy and consolidative surgery is still to be established⁴³.

LOCAL TREATMENTS AND ACTIVE SURVEILLANCE

The most studied ablative therapies (cryoablation and RFA) should be further refined and experimental local treatments require additional study. Active surveillance should be studied in comparison with other treatment modalities. Research is required to determine standardised surveillance strategies of treatments that limit unnecessary cost and radiation exposure without compromising cancer control⁶².

IMAGING AND RENAL TUMOR BIOPSY

Molecular image-guided surgery for kidney cancer is a promising treatment that requires further research⁶³. Newer imaging modalities may be useful in specific cases requiring more information on staging and tumour spread⁶⁴. The role and criteria for using renal tumour biopsy should be defined.

The impact of differences in regional funding and timely access to quality care/new treatments on patient outcomes needs to be evaluated in order to eliminate the disparities in kidney cancer care in the different countries.

RISK FACTORS AND CAUSES

The aetiology and risk (and protective) factors of kidney cancer are not completely understood. There is a need to develop research on lifestyles and their actual contribution to the forming of the risk factors and the resulting stratification of populations according to these risk factors. Researchers continue to look for foods and dietary supplements that can help lower RCC risk. The relationship of specific fruit and vegetable subgroups with RCC risk warrants further investigation. A recent meta-analysis supported the findings that cruciferous vegetables consumption was related to a decreased risk of RCC⁶⁵. Further well-designed studies are needed to better clarify the protective effect of cruciferous vegetables on RCC and potential mechanisms. Moderate alcohol consumption may have a favourable effect on RCC prevention^{66,67}. Analysis of the worldwide research on kidney cancer showed that consuming alcohol drinks (up to 30 grams = about 2 drinks a day) decreases the risk of kidney cancer (<http://www.wcrf.org>). But there is strong evidence that alcohol is linked to an increased risk of several other types of cancer. The mechanism for the association between moderate alcohol consumption and decreased risk of RCC is not well understood but several hypotheses have been postulated. Further research in the mechanisms involved is warranted⁶⁸. Genetic testing is available for more than a dozen of genes causing renal cancer. Advances in next generation sequencing will allow more comprehensive evaluations of common genetic variations. The options of RCC chemoprevention should be further explored and future research should focus on determining the target population.

The Kidney Cancer Research Network of Canada in collaboration with the James Lind Alliance, an international leader in setting research priorities identified the top ten research priorities in the management of kidney cancer. Patients, caregivers and clinicians were involved to reach consensus⁶⁹.

8. Maintaining a conducive EU research environment for kidney cancer

Innovative healthcare technologies and strategies are essential if we are to continuously improve the lives of Europeans affected by kidney cancer despite the financial pressures on healthcare systems.

It is crucial for the EU to continue to fund research on understanding diseases, diagnostic tools and innovative treatments to promote equal and fair access to for all Europeans affected by kidney cancer who would benefit from them to decrease the already high degree of inequalities in kidney cancer care and survival. The main barriers to access to innovation in oncology are reduced healthcare infrastructure and resources, lack of skilled healthcare professionals and complex regulatory and reimbursement pathways.

Practices or interventions that are inferior should be replaced by more efficient innovations that may deliver the best outcomes possible for patients within the limits of available resources. Improving access to innovation in care also requires greater involvement of patients and patient organisations in defining and assessing the value of innovation, giving adequate weight to quality of life and progression-free survival, and not only overall survival. Innovation must be guided by high-quality real-world data, including patient-relevant outcomes and actual costs of care⁷⁰. Sustained implementation of research is required to improve access to innovation in cancer care and ensure that all Europeans affected by kidney cancer benefit from a patient-centred multidisciplinary approach to integrated care.

The EU research and innovation programme, Horizon 2020, and its successor (FP 9) can support key areas of research for kidney cancer, such as prevention strategies, more accurate diagnosis and treatment (personalised medicine) and novel therapies.

9. The role of the European Association of Urology

For almost 40 years the EAU has addressed the most demanding issues on urological care in Europe, through its scientific and educational initiatives as well as its publications. Over 16,000 medical professionals are members and contribute to our mission: to raise the level of urological care throughout Europe and beyond.

A number of initiatives have been undertaken by the EAU to improve medical practice and care of patients with kidney cancer.

9.1 EDUCATION

The EAU provides the latest scientific evidence, expert recommendations and high-quality information on kidney cancer for medical professionals and patients (e.g. patient information leaflets in 11 languages). The European School of Urology (ESU) meets the educational needs of urologists on behalf of the EAU Education Office. Medical professionals benefit from online education, webinars, teaching courses and surgical training. The up-to-date information provided is in line with the EAU RCC Guidelines to guarantee consistency in content and quality.

9.2 EAU GUIDELINES AND PATIENT INFORMATION

The EAU Guidelines panel on RCC has prepared guidelines (www.uroweb.org/guidelines) that give an up-to-date overview of the available evidence for adequate detection, diagnosis, treatment and follow-up, to assist practicing clinicians in making evidence-based treatment decisions and improve patients' care. They are implemented and updated annually based on a structured literature search and systematic reviews. The RCC panel consists of an international multidisciplinary group of urological surgeons, medical and radiation oncologists, nurses, methodologists, a pathologist and a radiologist with particular expertise in the field of renal cancer care and a patient advocate.

Future updates of the EAU Guidelines will take into consideration the good clinical practice recommendations made by the European Commission's Joint Action on Cancer Control (CANCON) in relation to integrated cancer control, community-level cancer care, survivorship and rehabilitation, and cancer screening.

The EAU Guidelines in general and more specifically on kidney cancer have been endorsed by all the national urological societies of the 28 EU Member States and in many countries outside Europe including China, Australia, India, etc. The EAU embraces the involvement of stakeholders in Guideline development and has committed to a meaningful relationship with regard to priority setting and Guideline implementation⁷¹.

The EAU's Patient Information Initiative has produced the best easy-to-understand patient information leaflets on kidney cancer with the help of medical experts, patient groups and specialised nurses. The patient-oriented information is evidenced-based and consistent with EAU Guidelines.

EAU Patient Information offers detailed information on diagnosis and treatment of localised, advanced and metastatic kidney cancer as well as on palliative care and a dedicated section on practical and emotional support for patients and their relatives. A section with frequently asked questions about kidney cancer is also included. EAU Patient Information on kidney cancer is supported by educational images that show different stages of kidney cancer and illustrate the various treatment options.

EAU Patient Information on kidney cancer is part of the "EAU Patient Information Project" (<http://patients.uroweb.org>), which started in 2012 and has been translated into 17 languages so far, with the help of the national urological societies. It can be used by urologists/nurses as a tool for communicating with their patients.

9.3 THE ROLE OF PERSONALISED TREATMENT

The European Commission defines personalised medicine in a recent publication: "*Personalised medicine refers to a medical model using characterization of individual's phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) to tailor the right therapy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention*"⁷². New research on gene mutations linked to RCC (germline genetic mutations and acquired genomic events) may lead to the development of diagnostic and prognostic markers, risk-

stratification and more effective drugs that target those genetic changes (targeted therapy). These new personalised treatments may further improve clinical effectiveness and may have fewer side effects.

The combination of clinical criteria and clinically validated biomarkers might improve the personalisation of treatment in RCC patients. However, there are no validated biomarkers yet that can guide personalisation of therapy in patients with mRCC.

Examples of initiatives:

- The EAU organised a roundtable meeting on the subject in 2015 and recognised the need for personalised treatment in the treatment of urological cancers.
- The EAU is collaborating with the European Cancer Patient Coalition (ECPC) to increase awareness on the potential of precision treatment for kidney cancer to both European and national policymakers.
- The EAU is collaborating with the European Alliance for Personalised medicine (EAPM), who organised the first European Personalised Medicine Congress on 27-30 November 2017. The aim is to improve patients' care by accelerating the development and implementation of personalised medicine and diagnostics, through consensus.
- The EAU is chairing the Kidney Round Table organised by the International Centre for Parliamentary Studies (iCPS) in September 2018, where the European Commission, Members of the European Parliament, academic experts, clinicians, industry and patient groups team up to support national and EU-wide policy making on the overall management of kidney cancer in Europe.

9.4 FACILITATING ACCESS TO DIAGNOSIS AND TREATMENT - PATIENT-CENTRED MULTIDISCIPLINARY APPROACH

A close collaboration of multiple specialists in addition to urologists, such as medical oncologists, radiation oncologists, imaging specialists, nurses, pathologists, psychologists, nutritionists, physiotherapists, geriatricians, nephrologists and experts in palliative and supportive care is needed to ensure the best outcomes and quality of care for Europeans affected by kidney cancer and to lower the costs. Pre-defined coordination of the total care process, improvement in communication and clearly defined roles and responsibilities among all cancer care providers are required. Investment in adequate IT systems and adequate education of people with kidney cancer and health professionals is crucial. Primary care is well placed to have an expanded role in cancer control not only in prevention and diagnosis but also in shared follow-up, survivorship care and end of life care (Report from the ECCO 2017 Primary Care Track).

A patient-centred multidisciplinary approach is needed to decide which treatment options to offer to an individual, to minimise over-treatment of low risk disease and under-treatment of high-risk disease, to reduce the application of ineffective treatments in a given tumour type, to limit treatment costs by preventing treatment-related side effects, hospitalisation and loss of autonomy in older people, to tailor follow-up and handle survivorship. Patient-centred multidisciplinary cancer care is often not available in low-income countries because of reduced healthcare infrastructure, resources and skilled healthcare professionals but also by limited patient involvement in treatment decision-making.

Examples of initiatives:

- The European Multidisciplinary Meeting on Urological Cancers (EMUC) is an annual congress that aims to achieve consensus on controversial issues in diagnosis, risk-assessment and treatment strategies with the collaboration of the European Society for Medical oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the EAU.
- EAU RF study: European Active Surveillance of Renal Cell Carcinoma study <http://uroweb.org/wp-content/uploads/EASE-Facts-figures-07-03-2017.pdf>
- The EAU Update on Renal Cell Cancer (RCC) is an interactive educational meeting that takes place on a yearly basis. Scientific experts with a urological as well as a medical oncology background provide healthcare professionals with an update on the key topics of kidney cancer management.

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