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Treatment of Renal Cell Carcinoma in Elderly and Frail Patients

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1. Introduction

Renal cell carcinoma (RCC) is the most common cancer of the kidney (Motzer et.al., 1999). In the United States each year 57.000 new patients are being diagnosed with RCC resulting in 12.900 deaths (Linehan et.al., 2011). The median age at diagnosis today is 64 years and even though it represents only 3% of all cancers, the incidence is increasing steadily. With rising prevalence of some known risk factors like hypertension and population ageing, the incidence of RCC is expected to be rising even more in subsequent years. With increasing incidence of renal cell carcinoma (RCC) combined with population ageing, questions about the treatment of elderly and frail patients with RCC are becoming more and more relevant. Many of the patients with newly diagnosed RCC are in advanced age and/or have some major co-morbidities which often results in their poor performance status. Elderly or frail patients are frequently excluded from clinical trials, because the results of their treatment are often difficult to interpret. This is also true for patients with heart, lung, liver or other major co-morbidities. Excluding these patients from clinical trials leads to lack of evidence-based guidelines for their treatment and often poses to oncologists a difficult dilemma when they need to decide what treatment options to offer to patients (Scuch et.al., 2008). In the present chapter we would like to present current recommendations for diagnostics and treatment of elderly and frail patients with RCC. In the second part of the chapter results of the analysis of metastatic RCC patients treated in a single institution with emphasis on differences in the treatment between good and poor performance status patients are presented.

2. Age, performance status, co-morbidities and prognostic models

2.1 Age

Ageing is a complex process that affects every aspect of life. The US department of Health and Human Services Administration of Ageing estimates that 1 in every 8 Americans is older than 65 years. In 2006 this group represented 12,4% of the population, but by 2030 this number is expected to increase to 20%. With population ageing, incidence of all cancers is supposed to be rising in the next years and RCC is no exception (Neustadt et.al., 2008).

It is well known that the actual age is determined by physiology rather than chronology. Factors of biological aging include changes in the physical structure of the body as well as changes in the performance of motor skills and sensory awareness. These changes can lead

to multiple adverse events during the hospitalisation of an elderly patient especially in the postoperative period. Delirium episodes (acute decline of attention and cognition) can occur in 15-35% of patients during hospitalisation in the postoperative period and as high as 70-78% of patients in intensive care units. Prolonged hospitalisation is also associated with falls at rate 4-10/1000 patient-days. Other common adverse events are functional decline in 32% and adverse events of drugs in 10-15% of patients (Pushkar & Govorov, 2008).

Organs have a certain capacity to resist to stress and return to normal functioning after the stress on them has passed. This concept is termed "organ reserve". This reserve diminishes with age and may explain some functional deterioration in the elderly. Organ reserve in the young is supposed to be 7-11 times greater than in the advanced age person. Declining of organ reserve with age can not be predicted properly because it is subject to individual variation. Still, it has to be taken into account in treatment decision making (Neustadt et.al., 2008).

The patient's age is incorporated in the development of treatment decision and often is an inclusion /exclusion criterion of clinical trials. For a long time it was believed that older patients may tolerate treatment less well and may develop more adverse events compared to younger patients. Consequently, many treatments were not offered to older patients only on the basis of their chronological age without any strong evidence gained from clinical trials. It is becoming more and more clear that older patients may tolerate available treatments as well as younger ones and that treatments are being equally effective in both groups. Still, not all available treatments can be given without causing harm to all patients and some prudence is needed. Evaluation of functional organ reserve, evaluation of co-morbidities and performance status is of utmost importance (Calvo et.al., 2010).

2.2 Performance status

Beside accurate diagnostics and staging of tumours, before the decision on treatment modalities, performance status needs to be assessed in all cancer patients. Importance of pre-treatment performance status evaluation has been determined on the basis of several clinical trials that confirmed its prognostic value. Performance status can be assessed based on several different scales. In oncology the most commonly used are Karnofsky scale and the ECOG score (published by Oken et al. in 1982), also named WHO or Zubrod score. Scores and their comparisons are shown in Tables1 and 2.

Percentage	*Description*
100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requiring help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes

Table 1. Karnofsky performance status scale

WHO/ECOG	Description
0	Fully active, able to carry on all predisease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Table 2. WHO performance status scale

Karnofsky score of 90-100% corresponds to 0 on WHO scale, 70-80% to 1, 50-60% to 2, 30-40% to 3 and 10-20% to WHO grade 4. Patient death corresponds to 0% or 5 on Karnofsky and WHO scale respectively (Pushkar & Govorov, 2008).

Poor performance status in patients with RCC can be the result of one or multiple causes leading to a heterogeneous group of patients. Causes of poor PS (> 1 WHO) may be directly connected to RCC and metastases or may be the result of co-morbidities not directly connected to cancer (e.g. cardiovascular or hepatic diseases). Causes of poor PS related to tumour may be: pain from primary tumour or metastases, pleural effusion or ascites, brain metastases, anaemia, cachexia, gastrointestinal symptoms or fatigue (Pushkar&Govorov, 2008).

In measuring PS of the patient on WHO or Karnofsky scale some caution is needed because there are some situations where assessment of patient's functional status may require more than PS values written in numbers. For example, bone metastases: involvement of pelvis, femur or spine can force the patient to become bedridden, and the evaluation of PS in those patients can be difficult. Other criticism to the PS scales is that they do not include patient's nutritional status and they don't assess cachexia. Although performance status assessed with WHO or Karnofsky scales may not always reflect the actual functional status of the patient it is a most useful tool and should be utilized before and during the treatment of all cancer patients (Shuch et.al., 2007).

2.3 Co-morbidities

Outcome of therapy is depended not only on type and tumour aggressiveness but also on functional status of the patient and co-morbidities. In predicting possible outcome in elderly patients, evaluating performance status may not be enough and a thorough evaluation of their co-morbidities and organ functional reserve is mandatory. It is estimated that five years after the diagnosis of RCC, 30% of patients die because of conditions other than RCC. There are several ways to evaluate co-morbidities like American society of anaesthesiology (ASA) score used before surgery. Even though none of them is universally accepted, they may help us to determine the functional status of the patient (Pushkar & Govorov, 2008).

Evaluation of co-morbidities is and important part in the treatment decision process; but not only that, some of them may even predict the higher risk of developing RCC. The number of patients with end stage renal disease has increased markedly and haemodialysis is the most

widely used form of renal replacement therapy in the elderly. It has been demonstrated that patients on haemodialysis have a higher probability of developing RCC (Ishikawa et.al., 1990). The overall relative risk of RCC is 5-10-times higher in patients with end-stage renal failure (Levine et.al., 1992). To detect RCC early in the course of the disease, these patients should have regular urologic follow-ups. The incidence of RCC is also high in patients after kidney transplantation. Murphy reported that post-transplant patients have a 1,85 times higher risk of development of RCC that their matched controls in the general population. This higher risk was not affected by age, gender, ethnical group and time since transplantation (Pushkar & Govorov, 2008).

Neuzillet et.al. evaluated clinicopathologic characteristics and treatment outcome in 1250 RCC patients with end stage renal disease in comparison with RCC patients without end stage renal disease (ESRD). They found that ESRD patients with RCC were younger (55 vs. 62 years, $p<0,01$), were more frequently discovered incidentally (87% vs 44%, $p<0,01$), had less local and systemic symptoms and were males (76,5% vs 61,9%, $p<0,01$) at rate compared to RCC patients without ESRD. Tumours were detected at lower stage in patients with ESRD, had lower grade and were papillary higher in higher percentage (37% vs 7%, $p<0,01$) in ESRD. Interestingly, more patients with ESRD were in good performance status (ECOG 0) (76% vs 63%). Authors conclude that better tumour and patient's characteristics are the results of more abdominal imaging performed in these patients. Consequently, more incidental tumours are being diagnosed (Neuzillet et.al., 2011).

2.4 Prognostic models

In the treatment decision making process it is very important to predict the patient's survival. Patients with short predicted survival time should be evaluated carefully and best quality of life should be the primary goal of their treatment (Bukowski & Negrier, 2004).

Motzer et.al. conducted a retrospective trial to identify prognostic factors and to find predictive model of survival of patients with metastatic RCC. Pretreatment factors were evaluated. They identified five prognostic factors on the basis of which patients can be divided into three risk groups (low, intermediate or high) for which the median survival time was separated by six months. Patients with zero risk factors (low risk group) had median survival of 20 months, those with one or two risk factors (intermediate risk group), had median survival time of 10 and those with three or more risk factors (high risk group) had survival time of 4 months. The identified prognostic factors (called also Memorial Sloan Kettering prognostic factors) were (Motzer et.al., 1996):

- Lactate dehydrogenase levels > 1,5 times upper limit of normal
- Haemogloben level < lower limit of normal
- Corrected serum calcium level > 10 mg/dl (2,5mmol/l)
- Interval of less than a year from original diagnosis to the start of systemic treatment
- Karnofsky performance status < 80
- Absence of prior nephrectomy

In another trial conducted in the year 2004, Motzer evaluated survival in previously treated patients with metastatic RCC. 251 patients were included in the trial. Identified prognostic factors were:

- low (<80) Karnofsky performance status
- low haemoglobin levels
- high corrected serum calcium.

Based on these three factors he divided patients into three groups regarding their prognosis. The median survival in patients without any of the factors present was 22 months, with one factor 11,9 months and those with two or three 5,4 months. Even though his intent was to categorize patients into risk groups to better interpret the results of clinical trials, we can use this categorisation in assessing predicted survival in our every day clinical practice (Motzer et.al., 2004).

To evaluate Memorial Sloan Kettering prognostic factors, researchers at the Cleveland Clinic Taussig Center retrospectively evaluated 353 patients with metastatic RCC that were included in clinical trials between 1987 and 2002. Four of the five prognostic factors identified by Motzer were independent predictors of survival. In addition, prior radiotherapy and presence of hepatic, lung, and retroperitoneal nodal metastases were found to be independent prognostic factors. Using these expanded criteria, favorable risk is defined as zero or one poor prognostic factor, intermediate risk is two poor prognostic factors, and poor risk is more than two poor prognostic factors. Median overall survival times of these groups were 26.0, 14,4, and 7,3 months, respectively (P < ,0001) (Bukowski & Negrier, 2004, Mekhail et.al, 2005).

Different models predicting survival other than those developed by Motzer and Cleveland group have been proposed. Bamias studied prognostic factors in patients treated with sunitinib. He identified three prognostic factors: time from diagnosis to the start of sunitinib therapy, number of metastatic sites and performance status (Bamias et.al., 2010). Hudes et.al. in a trial with temsirolimus used slightly modified Motser's factors in selecting poor prognosis patients. Instead of absence of prior nephrectomy, metastases in multiple organs were included and Karnofsky performance status <70 was used (Hudes et.al., 2007).

2.5 Definitions of elderly and frail patients

Elderly population is not an uniform entity, since chronological and biological age can differ considerably (Neustadt et.al., 2008). On a basis of the observation that active oncological treatment can be outweighed by increased treatment toxicity in this patient population, age of 75 years was determined as a milestone for defining elderly patients population (Lane et.al., 2010). Frail patients are considered those in poor performance status (WHO>1) (Pushkar & Govorov, 2008). According to MSK model, patients with Karnofsky PS<80%had worse survival compared to patients with higher score (Motzer, et.al. 1996)

3. Tumour evaluation

3.1 Diagnostic procedures

In tumour evaluation, the diagnostic tests do not differ much between older and younger patient populations. In both groups CT is necessary for accurate detection of tumour and nodal extension. In patients with renal insufficiency, CT without contrast media or magnetic resonance imaging instead of CT is being performed in order to prevent further damage to kidneys by using a nephrotoxic contrast media. Abdominal ultrasound is another very

useful diagnostic tool that can easily be performed in all patients regardless of their age or performance status. The role of percutaneous tumour biopsy is limited in all patients. It may be of value in frail patients or in patients with overt metastatic disease to make a diagnosis of RCC and to avoid radical nephrectomy (Pushkar & Govorov, 2008).

3.2 Differences in tumour characteristics between young and elderly patients

Renal carcinoma is the most common renal parenchymal malignancy. Most of the patients are elderly with only 3-7% of RCC occurring in patients younger than 40 years. Trials performed in patients with breast, colon and prostate carcinomas showed that younger patients have a biologically more aggressive disease that leads to worse prognosis compared to elderly patients (Denzinger et.al., 2009).

To explore this issue in RCC, Denzinger retrospectively evaluated 1042 patients that were treated between 1992 and 2005. He compared patients younger than 45 years to patients aged over 75. In a multivariate analysis lower age was associated with higher 5-years cancer specific survival (95,2% vs 72,3% p=0,009) and lower 5-y progression rate (11,3% vs 42,5% p=0,002) (Denzinger et.al., 2009). Komai et.al. also found younger age to be a favourable prognostic factor. The 5-year cancer-specific survival rate was significantly better for the younger patients than for the older patients (p = ,049). Multivariate analysis showed that age was significantly associated with cancer specific survival (Komai et. al. 2011). Similar results were obtained in a trial of Jung and co-workers on low stage RCC patients (Jung et.al., 2009). These and other trials show uniformly, that younger RCC patients have better prognosis compared to the elderly (Denzinger et.al., 2009).

Trials also uniformly showed that younger patients are more likely to have a lower disease stage, lower nuclear grade, and smaller tumor size than older patients (Denzinger et.al., 2009, Komai et.al., 2011, Jung et.al., 2009).

4. Surgical treatment of elderly and frail patients

4.1 Radical and nephron sparing surgery in localized disease

Surgical resection is effective therapy for clinically localized RCC; with options including radical nephrectomy and nephron-sparing surgery. Radical nephrectomy (RN) was for many years considered the “gold standard” in the treatment of locally advanced RCC and nephron sparing surgery (NSS) was suggested when radical nephrectomy would render the patient functionally anephric. These cases included RCC in a solitary kidney, RCC in one kidney and the other non functioning and bilateral RCC (NCCN, 2011).

In recent years nephron-sparing surgery has become more and more popular (NCCN, 2011). Several trials showed that in patients with small tumours (<7 cm) the same oncological results can be achieved with NSS compared to RN (NCCN, 2011, Leibovich et.al, 2006, Becker et.al., 2006). In the trial of Leibowich the results of 91 patients treated with NSS and 841 patients treated with RN for 4 to 7 cm RCC between 1970 and 2000 have been compared. Cancer specific survival rates at 5 years for patients treated with NSS and RN for 4 to 7 cm RCC were 98% and 86%, respectively, the difference was not statistically significant (risk ratio 1,60, 95% CI 0,50-5,12, p = 0,430). Differences were not statistically significant even when authors compared the occurrence of local relapse or distant metastases (Leibovich et.al, 2006).

Nephrectomy (radical or nephron-sparing) should be considered as part of treatment decision process in all patients with stage I-III disease fit for surgical procedure (NCCN, 2011). In elderly or poor performance status patients still amenable for surgery nephron-sparing nephrectomy rather than radical nephrectomy should be performed whenever possible (Lane et.al., 2009). In patients with decreased life expectancy and/or extensive co-morbidities, surgery represents excessive risk and other options like tumour termoablation or active surveillance should be considered (NCCN, 2011)

4.2 Cytoreductive nephrectomy in patients with metastatic disease

Multimodality treatment in patients with metastatic RCC consists of surgery combined with systemic therapy. Surgical approach consists of cytoreductive nephrectomy often combined with metastasectomy of distant metastases. This approach in cancer therapy is distinctly different from treatment of other types of cancer. The rationale for nephrectomy is multiple: enhancing the effects of systemic therapy, removing the source of distant metastases and providing additional tissue for evluation in targeted therapy (Kutikov et.al., 2010).

To assess the benefit of cytoreductive surgery in patients with poor performance status (PS WHO 2 or 3), Shuch et.al. performed a retrospective analysis of all patients who underwent CN surgery at the University of California in between 1989 and 2006. They compared the results of patients in good (WHO 0,1) with those in poor performance status (WHO 2,3). Patients with poor PS had shorter disease-specific survival compared to patients with better PS (6 months vs. 27 months). Systemic treatment in CN was administered to only 57,5% of patients in poor performance status and no objective response was seen in these patients. CN in these patients may be used only to palliate haematuria or pain, but survival benefit of CN in poor PS patients is limited. (Scuch et.al., 2008, Kutikov et.al., 2010, Pushkar & Govorov, 2008, Chouieri, 2010).

Cytoreductive surgery should be offered to patients in good performance status only. Beside these, patients with lung metastases only and those with good prognostic features benefit most from it. The role of CN in the era of targeted therapy has not been defined jet. Randomized trials are ongoing and should answer this dilemma (NCCN, 2011).

4.3 Observation and palliative surgical aproaches

Observation (so called watchful waiting or active surveillance) is a less aggressive treatment modality and should be considered as an option in elderly patients with or without major co-morbidities, especially those with small incidentally found tumours and in those with larger tumours, but very short life expectancy. For the latter, surgery represents a greater risk compared to observation alone. Kassouf et.al. demonstrated that observation is a safe option, most of the tumours observed did not show signs of growth and none of the 24 patients in the trial developed metastases during the 31.6 months of median follow-up (Pushkar & Govorov, 2008).

One question still open is whether to perform tumour biopsy to prove malignity before active therapy is delivered. In the past this approach was not frequently adopted, mainly because a lot of false negative results found and because of the fear of side effects connected to biopsy of renal mass. In recent years renal biopsy became relevant. This is due to the fact that 20% of small renal tumours are benign or have low malignant potential. Biopsy should

be considered whenever some doubt exists in decision to perform surgery, minimally invasive procedures or to observe the patient (Lazzeri et.al., 2010).

Paliative nephrectomy should be considered in patients with gross haematuria or other symptoms related to primary tumour that can not be controlled by non invasive measures, like uncontrollable pain (NCCN, 2011). Moreover, it may palliate pain and treat paraneoplastic syndromes associated with metastatic RCC (Kutikov et.al., 2010).

Tumour transarterial embolisation (TAE) in RCC patients has an established role in palliative treatment. It can be used to diminish patient's suffering from pain, haematuria or paraneoplastic symptoms. It can be offered as a sole treatment option or preoperatively to diminish the blood loss during nephrectomy. Although it is considered a palliative measure, 80% of patients to whom TAE has been performed, remain disease free after the procedure (Lane et.al., 2010). TAE should be offered to patients with short life expectancy, since neovascularisation is expected to occur some time after the procedure (de Reijke et.al., 2010). Munro et.al evaluated 25 patients treated with TAE. In this survey TAE was performed in two groups of patients. The first group consisted of patients with stage IV disease (median age 73 years) and the second of mainly elderly (median age 80 years) patients stage I-III disease who were unable or unwilling to receive nephrectomy. Authors analysed the usefulness of TEA regarding symptom control, hospital stay and survival. The conclusion was that embolisation is a good treatment option for palliating symptoms derived from primary tumour in patients with advanced disease and those with localized disease and poor general condition (Pushkar & Govorov, 2008). Other palliative measures available today are cryoablation, radiofrequency ablation, high-intensity focused US; microwave thermotherapy and radiosurgery. Results with all these techniques, even if studied in trials with small included number of patients, are promising not only in terms of palliation, but also in terms of disease free and cancer related survival (Lazzeri et.al., 2010).

5. Systemic therapy of metastatic disease

Despite advances in RCC detection, still 20-30% of patients present with metastatic disease. Treatment of metastatic disease in elderly and frail patients represents a big challenge for medical oncologists. Until recently there was a widely accepted belief that the treatment may not be effective in older patients and that they may be at higher risk of developing adverse events than younger patients. Consequently, they were often excluded or inadequately represented in clinical trials. However, recent evidence indicates that available treatments may be tolerated and effective in all patients regardless of age. Metastatic RCC is a chemotherapy resistant disease and until recently treatment options of these patients were limited. With the development of targeted therapies, new treatment options became available. Yet the question of efficiency and tolerability of this agents in elderly and frail patients arose (NCCN, 2011, Scuch et.al., 2008).

5.1 Treatment with immunotherapy

Immunotherapy with interferon alfa and interlekin-2 was for a long period the cornerstone of systemic treatment of metastatic RCC. Nowadays immunotherapy is being successfully replaced by less toxic and more effective targeted therapies. Trials performed with immunotherapy have shown that patients with worse performance not only had

shorter survival, but also had a decreased response rate to immunotherapy and greater frequency 3 and 4 toxicity. Decreased response to immunotherapy is supposed to be due to the fact that patients with PS>1 have a compromised immune system; immunotherapy success is clearly related to a good immune system. Nevertheless, it is difficult to determine whether the treatment is less effective because the performance status is low or whether the performance status is low because tumour is more aggressive (Pushkar & Govorov, 2008). This, together with tumour characteristics, is the reason why immunotherapy was not approved in the treatment of patients with poor performance status (Scuch et.al., 2008).

5.2 Treatment with targeted therapies

In recent years a whole new spectrum of treatments with targeted drugs became available in the treatment of metastatic RCC. These new drugs were tested to treat elderly and frail patients with promising results (Bellmunt et.al., 2011).

Sunitinib targets a number of receptor tyrosine kinases including platlet-derived growth factor receptors, vascular endothelial growth factor receptors, stem cell factor receptor, FMS-like tyrosine kinase, colony stimulating receptor and neurotropic factor receptor (NCCN, 2011). Sunitinib has established role in the treatment of metastatic RCC (Gore et.al., 2009). The efficacy and safety of sunitinib in elderly and poor prognosis patients was assessed in an expanded-access trial. Of 4371 included patients 582 (13%) had PS 2 or higher and 1418 (32%) were aged 65 or more. Results showed a 17% objective response rate in the elderly and a 9% rate in PS≥2 patients. Median progression free survival was 11,3 months (95% in elderly and 5,1 months in poor performance group). Side effects were few and tolerable. Authors concluded that sunitinib is effective and safe even in groups of patients that are supposed to tolerate treatment less well and are usually excluded from clinical trials (Gore et.al., 2009, NCCN, 2011, Calvo et.al., 2010).

Sorafenib is a small molecule that inhibits multiple tyrosine kinase receptors (NCCN, 2011). Treatment with sorafenib is considered to be equally effective in elderly and younger patients. Retrospective subgroup analysis of data from TARGET (Treatment Approach in Renal Cancer Global Evaluation) trial showed similar clinical benefit in patients aged 70 years or more compared to younger ones (83,5% in older and 84,3% in younger patients) (Calvo et.al., 2010). Incidence of adverse events were not significantly higher in elderly patients receiving sorafenib. Thus sorafenib represents an important treatment option for elderly patients with RCC (Dutcher et.al., 2010).

Temsirolimus was tested in a phase 3 trial comparing it to interferone therapy in patients with poor prognosis. Patients included in the trial had at least three of the 6 criteria for poor prognosis according to the modified MSCC. Patients were randomized to one of the three arms (temsirolimus alone, interferone alone or both treatments given together). Patients that received temsirolimus alone had longer overall survival compared to other two groups. (OS 10,9 months temsirolimus alone, 7,3 interferone, 8,4 combination). The main conclusion of this trial is that treatment with temsirolimus alone leads to moderate prolongation of survival compared to treatment with interferon in patients with poor prognosis. Based on this trial, temsirolimus is indicated in the first line of therapy in poor prognosis patients (Hudes et.al., 2009, Rejike et.al., 2010).

Bevacisumab is an recombinant humanized monoclonal antibody that binds and neutralizes circulating VEGF-A. Bevacisumab was approved by FDA for first line treatment in combination with IFN-α (NCCN, 2011). Concerns about administering bevacisumab in elderly, have been diminished by retrospective trials that showed similar efficacy and toxicity profiles compared with younger patients. Billemont et.al. presented data regarding treatment of elderly patients with all antiangiogenic therapies (sunitinib, sorafenib, bevacisumab). There were no toxic deaths, most common grade 3 or 4 were skin toxicity and mucositis. Authors conclude that antiangiogenic therapy including bevacisumab, can be administered safely to patients older than 75 years (Billemont et.al., 2010). Other retrospective trials similarly conclude that side effects, while more pronounced in the elderly, are well tolerated and not dose-limiting (Calvo, 2010).

Pazopanib is an oral VEGFR-1 and 2, PDGFR-α and β. It was approved for treatment of metastatic RCC in 2009 (NCCN, 2011). The most common side effects of pazopanib are diarrhoea, fatigue and hair depigmentation. The most worrying side effect is hepatotoxicity grade 3 present in 12% aldough fatal events are rare (0,05% of cases). Even if only 6% of patients included in the trials with pazopanib were aged > 75 years, no differences in safety and effectiveness was observed in comparison with younger ones (Calvo et.al., 2010, FDA, 2009, Bukowski, 2011).

Everolimus is an inhibitor of mTOR. It was approved for the treatment of metastatic RCC after failure of sunitinib or sorafenib in 2009 based on a phase III trial named RECORD 1 wich compared treatment with everolimus to placebo (NCCN, 2011). To assess the efficacy and safety of everolimus in elderly patients (>70 years), Hutson et.al. performed an exploratory analysis of RECORD-1 trial data. Everolimus prolonged PFS in this group of patients, compared to placebo. Some adverse events (eg, cough, diarrhea, asthenia, fatigue) were more frequent in the elderly subset vs. the overall RECORD-1 population (median age, 61 y); but this is likely related to the intrinsic characteristics of this subpopulation, given that these adverse events also were more frequent in the elderly subgroup receiving placebo (Hutson et.al., 2010).

According to the data obtained from trials published until now, most of the targeted therapies are equally effective and safe in elderly and/or frail or in young and good performance status patients. In most cases dose reduction is not necessary and some of the targeted therapies (i.e. everolimus) may even prevent worsening of renal function in transplant patients and those with multiple co-morbidities. The conclusion of multiple trials is that newer targeted drugs should be offered to elderly and/or patients with multiple co-morbidities. It can not be stressed enough that including these patients in clinical trials is mandatory (Calvo et.al., 2010).

6. Treatment with radiotherapy

In the rare case of inoperable RCC, radiotherapy can be administered with promising results. In a trial of Wersall, 58 patients with inoperable or metastatic RCC received high dose stereotactic radiotherapy (32Gy in 4 fractions, 40Gy in 4 fractions or 45Gy in 3 fractions). Partial response or stable disease was observed in 90% of patients and local control rate of 90-98% was achieved. Radiotherapy can be safely administered to elderly and frail patients and should be considered whenever radical therapy is not applicable (Wersall et.al., 2005, de Rejike et.al., 2010).

For patients with brain metastases, radiotherapy has an important role in their treatment. Using stereotactic radiotherapy similar results can be achieved as with surgical removal of brain metastases. The stereotactic radiotherapy is non-invasive, outpatient and can be applied in patients in lower PS, without worsening their condition (de Rejike et.al., 2010).

Bone metastases represent a special problem. Patients with bone metastases are often symptomatic; pathological fractures, spinal cord compression and the need for surgery are common, and nearly 80% of untreated patients experience skeletal-related events. Until recently treatment options for these patients were scarce because of the chemo and ratio-resistance of RCC. With the development of new agents like biphosphonates and targeted agents, better results in treatment of bone metastases regarding pain control and pathologic fractures can be achieved. Yuasa showed that combining radiotherapy with biphosphonates administration leads to higher objective response and less skeletal related events compared to radiation therapy alone. In administering biphosphonates caution is needed because of the renal impairment (Yuasa et.al., 2010).

7. Treatment of elderly and frail metastatic RCC patients at the Institute of Oncology Ljubljana

To explore the treatment approach in every-day practice we retrospectively evaluated T_{any} N_{any} M1 RCC patients that were treated at the Institute of Oncology Ljubljana, Slovenia, between 2006 and 2009 and for whom appropriate data were available. A patient was considered to have a metastatic disease if it was confirmed by biopsy or clear signs of metastatic disease were present on radiographic evaluation. Staging was performed by using CT imaging of thorax and abdomen. If needed other diagnostic tests were performed. Surgical procedures were done in hospitals other than Institute of Oncology. Performance status was assessed according to WHO scale. The aim was to assess possible differences in the treatment strategy decisions in good (WHO 0 or 1) versus poor (WHO>1) performance status patients.

Medical records of 368 patients were reviewed. Patients with incomplete records were excluded. Patient and tumour characteristics are presented in Table 3.

Variable	*Metastatic RCC patients No=368*
Male	268 (72,8%)
Female	100 (27,2%)
Median age	63.3 (34-86) years
Histology	
Clear cell	228 (62%)
Papillary	37 (10,0%)
RCC not other specified	64 (17.4%)
Sarcomatoid	26 (7,1%)
Other rare (chromophobe, collecting duct, mixed…)	13 (3,5%)

Performance status	
0	89 (24,2%)
1	108 (29,3%)
2	57 (15,5%)
3	70 (19,0%)
4	38 (10,3%)
Unknown	6 (1,6%)
Co-morbidities	
Present	93 (25,3%)
Absent	262 (71,2%)
Unknown	13 (3,5%)

Table 3. Patient and tumour caracteristics

All patients were reviewed by the multidisciplinary board that consists of an urologist, a medical oncologist and a radiation oncologist. All patients had proven metastatic disease before presentation to the board. Administered treatment is shown in Table 4.

Treatment mode	*Number of patients treated (percentage)*
Surgery	
Nephrectomy with radical intent (performed before metastatic disease was present)	162 (44,1%)
Cytoreductive nephrectomy	106 (28,8%)
Tumour embolisation	43 (11,6%)
Systemic therapy	
Immunotherapy	50 (13,6%)
Targeted therapy	156 (42,4%)
Watchful waiting	12 (3,3%)
Best supportive care	150 (40,0%)

Table 4. Treatment options

To establish possible differences in the decision of treatment strategy in different groups of patients, a comparison was made. All treatment decisions were made by a multidisciplinary

team of oncologists on the basis of medical documentation and clinical examination of the patient by a member of the team. Comparison between groups was done with X^2 test. Differences between patients in good vs. poor performance status, patients with or without major co-morbidities and younger vs. elderly patients is shown in Table 5.

	Systemic therapy (immunotherapy or targeted therapy)	*Best supportive care or observation*	
Performance status			
PS 0,1	179 (90,8%)	18 (9,2%)	
PS>1	26 (15,7%)	139 (84,3%)	p<0,01
Co-morbidities			
Not present	160 (61%)	102 (39%)	
Present	50 (53,7%)	43 (46,3%)	p=0,76
Age			
< 75 years	151 (72,7%)	57 (27,3%)	
≥ 75 years	12 (7,5%)	148 (92,5)%	p<0,01

Table 5. Differences in treatment decisions

As expected, the patient's performance status has an important impact on treatment decision. Patients in good PS receive systemic therapy in much greater percentage of cases than patients in poor PS. Patients in poor PS are more likely to tolerate less well systemic therapy and treatment decisions in every-day practice reflects the knowledge of this fact. Defining PS, even if it is a subjective measure, is very important and should be made by an experienced clinician. Still, some patients in good PS do not get the systemic therapy and some in poor PS get it. This reflects the influence of other factors, like age of the patients and co-morbidities on treatment decisions.

The difference between treatment decisions based on co-morbidities is not clear. In our review, systemic treatment was administered to many patients with co-morbidities. An explanation for this is, that according to known data, most of the available targeted therapies are effective and safe for the majority of patients with co-morbidities. Nevertheless, half of the patients with co-morbidities present do not get the specific therapy.

With evolving results from clinical trials, new data on safety and efficacy will become available which will help clinicians in treatment decisions.

Age has a huge impact on treatment decisions. Less than 10% of metastatic RCC patients older than 75 years get systemic therapy prescribed. Prescribing targeted therapies to elderly patients still represents a challenge to clinicians. This is in accordance with the widely established tendency to believe that older patients tolerate the treatment less well and develop adverse events in higher percentage and at greater degree. Recent evidence shows that available treatments (targeted therapy) are safe and efficient in elderly as well as young patients (Calvo et.al., 2010).

8. Conclusions

Longer life expectancy together with the growing incidence of RCC has raised the number of elderly and frail patients with this malignancy. Tailoring treatment to the individual patient according to the tumour stage and patient general condition is the primary goal of treatment. Treatment options for the elderly and frail are multiple and vary in their aggressiveness. Finding the right treatment for the right patient can be a difficult task for oncologists. Improvement in all fields from surgery to targeted therapies led to broader treatment choice. The problem that remains is that often no evidence exists which treatment combination to use, since much too often these patients are excluded form clinical trials. How to encourage investigators to design clinical trials so as that these patients can be included in greater numbers, remains a difficult open question especially in large trials testing new drugs. Conducting trials addressing these populations after the drug has been approved for use in good prognosis-good performance patients deprives others of a new drug which is often well tolerable and effective.

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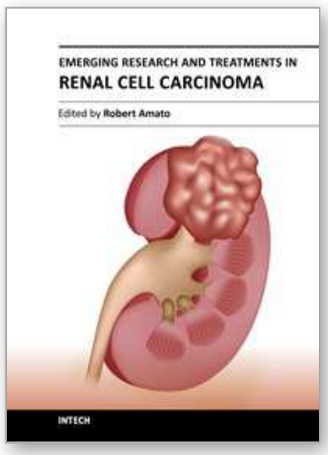

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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

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