

Asymptomatic Kidney Tumors in Elderly Patients: Review of Treatment Approaches in Russia and Western Countries

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Received November 20, 2018; revised November 30, 2018; accepted January 10, 2019

Abstract—This paper analyzes and evaluates the results of recent research on active observation strategies in North America and Europe. There are enough grounds for a more active implementation and use of this approach, which is permissible in a strictly selected category of patients, namely, in elderly patients. In Russia at the moment, the personalized approach to treatment is underdeveloped. Patients over 60–65 years old are a significant group of patients with kidney tumors. In the determination of the tactics of the care of these patients, it is important to understand that this contingent has a greater risk of death from comorbidities than the relatively low risk of death from kidney cancer. The improvement of modern diagnostic methods and the introduction of screening programs have led to a significant increase in the frequency of the detection of small kidney tumors in elderly patients. The results of studies comparing radical approaches to treatment and observation suggest the widespread adoption of a strategy for the active monitoring of asymptomatic kidney tumors in the elderly in Russian oncological practice.

Keywords: renal cell carcinoma, asymptomatic tumors, active observation

DOI: 10.1134/S2079057020010051

INTRODUCTION

More than 200 000 new cases of renal cell carcinoma (RCC) are registered annually in the world—2.2% of all malignant diseases in men and 1.5% in women. More than 90% of all malignant kidney tumors are RCC [25]. The trend of an increase in the absolute number of patients with renal cell carcinoma persists, and, therefore, the freshness of views on approaches to treatment remains relevant. global incidence of RCC varies between 3–13 per 100 000 people, has a pronounced geographical fragmentation and can vary significantly in different countries (more than 20 times in men and 15 times in women) [25]. In Russia, more and more patients with malignant neoplasms of the kidneys are taken annually for cancer registration. At the moment, this figure has already overcome the threshold of 20 000 new cases per year. In the structure of morbidity, kidney cancer makes up 3.9% of the total number of newly diagnosed cancer patients [4].

The highest rates of RCC incidence in the world are recorded in developed Western countries, namely, in the United States, Europe, and Australia. The lowest incidence rates are observed in Africa and Asia, India, Japan, and China [11, 13, 14, 30]. This pathology is detected in men three times more often than in women. More than 65 000 new cases of kidney cancer and more than 14 000 deaths from this disease have

been registered in the United States over the past ten years, which is approximately 4% of all cases of newly diagnosed malignant neoplasms [30, 32]. The forecasts of the American Cancer Society (ACS) annually increases. Among European countries, Great Britain stands out as the country with the most well-organized registration system for cancer patients. For example, the RCC incidence in this country in men and in women was approximately 19 and 11 per 100 000 people, respectively. Patients over the age of 60 constitute 75% of kidney cancer patients in the United Kingdom.

The RCC incidence increases from the age of 40 years, reaching the upper limit in patients older than 80 years [12]. In general, indicators around the world demonstrate a steady increase in RCC incidence—approximately 2–3% per ten years. Thus, the incidence rate more than doubled in England for the period from the mid-1970s to 2010. In this case, Poland, Sweden, Denmark, and Finland, where the incidence rates have, on the contrary, decreased in recent years, are the exception. In the United States, the annual increase in RCC incidence is recorded to be approximately 1.7% in men and 2.2% in women [12, 21].

The global RCC mortality rate is more than 130 000 cases annually. In men, this level is two times higher than in women. The RCC mortality rates are highest

in the United States, Canada, and the countries of Western Europe. The lowest rates are recorded in the countries of Asia and Africa. In the United Kingdom, RCC is in 10th place among men and 12th place among women among the causes of mortality from malignant neoplasms. Eighty five percent of deaths occur in elderly patients whose age exceeds 65 years [13]. An increase in mortality rates from malignant kidney tumors was noted in European countries until the 1990s, but it began to stabilize and decline closer to the end of the century. In the United Kingdom, the RCC mortality rate increased from the early 1970s until 2010 (from 4.3 to 6 in men and from 2.1 to 3.1 in women per 100000 people); over the past five years, the indicators have shown stabilization [12]. A decrease in mortality rate was noted in the Scandinavian countries since the 1980s and from the early 1990s in France, Germany, Austria, and Italy. Meanwhile, an increase in RCC mortality rates is recorded in a number of European countries (Greece, Ireland, Slovakia, and Croatia) [26].

The survival rates in RCC patients have a positive upward trend. Thus, the five-year survival rates in the United Kingdom over the past 30 years have increased in men from 28 to 53.3% and in women from 28 to 54.8%. At the same time, it is important to note the age dependence of the five-year survival indicators: for men, from 70% at the age of 18–50 years to 31.7% at the age of 75–99 years; for women, from 72% at the age of 18–50 years to 29% at the age of 75–99 years [11, 20, 31]. The five-year survival rate for RCC patients in the United States has increased significantly over the past 50 years. In the 1960s it was 40%, and it is now 71%.

According to the dynamics of the increase in incidence over a decade, kidney cancer in both genders is in the second place, following malignant tumors of the brain and other parts of the nervous system (in third place for men and in second for women). The approximate indicator has increased from 9.37 per 100000 people to 13.19; thus, the increase amounted to 40.85% at an annual growth rate of 3.48% [31]. This is due to the widespread introduction of modern imaging methods and routine dispensary examinations of the abdominal cavity, where the kidneys fall into the study area. In this connection, the proportion of accidentally detected, small-sized kidney tumors has also increased. Kidney tumors are an accidentally discovered finding during clinical examination in 80% of cases around the world. The percentage of accidentally detected kidney tumors has increased from 7–13% in the 1970s to 49–69% at present [23, 24].

One feature of the course of this disease is its asymptomatic nature, almost until the last stage. The clinical picture, according to which kidney cancer was previously diagnosed (macrohematuria, lumbar pain, palpable tumor), is currently found in no more than 10% of cases. Paraneoplastic symptoms, which

include weight loss, arterial hypertension, fever, and changes in laboratory parameters, are determined in approximately 35% of cases. In 20–30% of patients, the diagnosis is established in the already aggravated form. Thus, an asymptomatic kidney tumor can be detected by chance at any diagnostic stage. The diagnosis is established in this case at an early stage, when the patient does not feel any clinical manifestations. The positiveness of this aspect is more important for younger patients, while the accidental detection of an asymptomatic kidney tumor in an elderly patient can become a significant, primarily psychological problem, due to the features of the treatment of this pathology. The specifics of the treatment of malignant tumors in elderly and senile people and their rehabilitation are receiving more and more attention every year. Geriatric oncology has become one of the rapidly developing areas in modern science [2].

REVIEW OF THE RESULTS OF STUDIES ON OBSERVATION AND APPROACHES TO THE TREATMENT OF KIDNEY CANCER IN ELDERLY PATIENTS IN RUSSIA AND WESTERN COUNTRIES

It is an increase in the incidence of kidney cancer that caused the rise in the number of surgical interventions on account of this disease. Surgical treatment remains the standard tactical approach for all clinically localized kidney tumors. According to medical statistics, the proportion of surgery as an independent type of treatment is growing steadily. In 2016, it amounted to 54.3% (53.7% in 2015). High rates of the use of the surgical method as an independent type of radical treatment are observed specifically for kidney cancer (92.6%) [3]. The latest recommendations of the European Association of Urology for patients with an established diagnosis of T1a–T1b stage kidney cancer with a tumor size of less than 4 cm suggest an organ-preserving surgery—a kidney resection. At the moment, it is a universally recognized standard for surgical treatment and, due to the improvement in laparoscopic and robotic technology, it is increasingly often performed with minimally invasive entry [15]. However, the widespread use of laparoscopic organ-preserving surgery is still limited and is not accessible everywhere due to the complex technique, skills, the need for training, and the demand for a large patient flow, which is mainly possible only at large clinics. Global recommendations serve as the basis of clinical recommendations in Russia, where organ-preserving, high-tech, surgical interventions are given the highest ranking (Table 1) [1].

However, it should be understood that, despite the improvement in surgical techniques, surgery, whatever it is, is always a high risk and significant stress for elderly patients. Active observation has only recently begun to be mentioned in clinical guidelines as an alternative to aggressive surgical tactics (Table 2).

Table 1. Russian recommendations for the treatment of localized and locally advanced renal cell carcinoma (RCC)

Recommendation	Credibility	Level of recommendation
Surgery is the only radical treatment for RCC	—	C
For tumors of stage T1, kidney resection should be performed if possible	3	B
In the presence of appropriate technical capabilities, kidney resection is a standard procedure for solitary kidney tumors with a diameter of <7 cm	3	C
In case of kidney resection, a minimum space must be left within healthy tissues to prevent a local relapse	—	B
Extended lymphadenectomy is not recommended for all patients due to the lack of data on improved survival	1b	A
Extended lymphadenectomy should be performed for staging in patients with palpable and/or enlarged lymph nodes		
Adrenectomy is not recommended for patients with normal adrenal glands according to preoperative CT examinations and in patients in whom an intraoperative examination does not reveal metastases in the adrenal gland or a direct growth of the tumor into the adrenal gland	3	C
There is a high risk of the development intrarenal relapse in patients with large tumors (>7 cm) or in the presence of a positive edge of resection after organ-preserving surgery	3	—
Laparoscopic radical nephrectomy is recommended and is the standard in the treatment of RCC patients of stage T2 and in patients for whom kidney resection cannot be performed	—	C
Laparoscopic radical nephrectomy is not recommended for patients with tumors of T1 stage; kidney resection is recommended for them	3	C
Open kidney resection remains the standard of care today	—	C
Laparoscopic and robot assisted kidney resection are alternative options of open kidney resection	—	C

Table 2. Surgical treatment of a primary tumor depending on category T

Category	Operation type	Entry	Use
T1a	Organ-preserving	Laparoscopic	Treatment standard
	Radical nephrectomy	Open	Justified for specific indications
		Laparoscopic	
T1b–T2	Organ-preserving	Laparoscopic	Treatment standard
	Radical nephrectomy	Open	Adequate recommended volume associated with more severe pain
T3–T4	Radical nephrectomy	Open	Standard for most patients
		Laparoscopic	Possible for a limited contingent of patients

The age at the time of the establishment of the initial diagnosis in almost 50% of patients exceeds 65 years (Table 3). It is important to note that, according to the data of the Federal State Statistics Service, the average life expectancy was 72.4 years in 2017. According to this indicator, Russia is not included even in the top hundred countries of long-lived people (Table 4) [4].

Of course, this group of patients has a high frequency of concomitant diseases, and the risk of death from cardiovascular pathology or some other concom-

Table 3. Average age of patients with the first established diagnosis of malignant kidney tumor in Russia in 2006 and 2016 [4], years

Gender	2006	2016
Both genders	61.3	62.4
Men	60	61
Women	62.9	64.1
Differences of the average age in women and men	2.9	3.1

Table 4. Average age of deaths from malignant tumors in Russia in 2007 and 2017 [4], years

Gender	2007	2017
Both genders	65.1	67.7
Men	63.3	65.7
Women	68.2	71

itant pathology can significantly exceed the risk of death from RCC. In addition to patients with a high operational and anesthetic risk, there is also a group of patients that refuse surgery for one reason or another.

To date, a small number of reports have been published regarding the course of clinically localized RCC in patients who have not received treatment. However, according to the results of studies on this issue, it can be stated that the identification of a localized tumor process characterized by a favorable course and prognosis occurs increasingly often. All of these studies have been carried out only by Western colleagues, although it should be recognized that, due to the low indicators of average life expectancy, less aggressive surgical approaches and a more personalized approach to a patient would be more relevant for Russia. The bulk of newly diagnosed kidney tumors are accidentally detected, asymptomatic small (less than 3–4 cm) kidney tumors without signs of distant metastases. This class of tumors is usually represented by a more highly differentiated structure than tumors that are detected in case of clinical manifestations. It should be noted that, according to postoperative pathological studies, 40% of tumors are benign. If we talk directly about the malignant variant of a kidney tumor, then the gradation of the atypia of the cell nucleus proposed by Furman is the most common system for the assessment of the degree of RCC malignancy. The following types of RCC are morphologically distinguished: light-cell (80–90%), papillary (10–15%), and chromophobic (4–5%), and collecting duct cancer (1%).

There is also a low frequency of local relapses after organ-preserving surgery for RCC, which once again confirms the low malignant potential of many tumors.

Currently, up to 60% of newly diagnosed kidney tumors are asymptomatic and are a consequence of the availability of routine diagnostic procedures and in some cases are due to a phenomenon such as overdiagnosis. Approximately 15–20% of solid kidney tumors are benign, while more than 30% of the observed neoplasms do not increase in size [16, 27].

Based on the extensive experience of monitoring elderly patients with RCC, it is generally accepted that the progression of the tumor process in them is rather slow in most cases. A number of studies have shown that even malignant tumors confirmed by histological examination are not prone to aggressive course. These studies most often evaluated the tumor size, the

growth rate, the potential for metastasis, and the dependence of the growth rate on patient age.

Breakthrough results on this issue were presented in 2013 in the United States (Orlando) at the IV Annual Symposium on Combating Genitourinary Cancer [28]. Researchers conducted a large retrospective study that included more than 8000 patients over the age of 65 whose kidney tumor size did not exceed 4 cm at the time of diagnosis. The patients were singled out for seven years (since 2000). The study was conducted as part of the Surveillance, Epidemiology, and End Results Program (SEER).

Surgical tactics were the main treatment option. Surgical interventions were performed in 70% of patients; another control group consisted of 30% of patients who remained under active observation. Over the seven-year observation period, the percentage of patients for whom observation tactics were chosen increased from 25 to 37% ($p < 0.001$) [28].

Within six months after diagnosis, a trend towards improved survival was observed in patients undergoing surgical treatment. Then, in the period from 6 to 36 months, the survival vector changed and became positive for the patients of the observation group (in general, the risk of death for this group decreased to 30%). No significant differences were found by the researchers between the surgical treatment group and the active observation group. It is also necessary to note the low percentage (3%) of deaths from kidney cancer in case of the five-year observation period. Patients in the active observation group had a significantly lower risk of death regardless of its cause than the surgical treatment group [28].

M.A.S. Jewett et al. obtained quite interesting results from a prospective study on active observation tactics conducted in 2004–2009 [16–19]. In eight clinics in North America, the prospective study of phase II included 178 patients; the mean age was 73 years, and the average tumor size was 2.1 cm. All patients participating in the study either had significant contraindications to surgical treatment or independently refused it for some reasons. An increase in tumor size by more than 4 cm or the appearance of a metastatic lesion was considered a sign of progression in this study. Of the patients, 127 were observed for more than 12 months. Some (99) patients underwent morphological verification in the form of tumor biopsy. RCC was histologically confirmed in 56 (55%) patients, benign tumors were detected in 12 (12%) patients, and the biopsy was uninformative in 33%. The total tumor growth rate was 0.13 cm per year, and it should be noted that there were no significant differences between the groups of malignant and benign tumors ($p = 0.8$). Of 37 morphologically confirmed RCCs, ten (27%) tumors decreased in size over the observation period, and progression was observed in the remaining 27 (15.2%) cases. Of these, 13 (7.3%) patients showed an increase in tumor size by more

Table 5. Results of studies on active observation [5–10, 19, 27, 29]

Authors of the study, year	Number of patients	Age	Indications	Average tumor size, cm	Observation period, months	Growth rate, cm/year	Growth rate parameter
R. Abouassaly, 2008	110	81	>75 years	2.5 (0.9–11.2)	24	0.26	43% without trend towards growth
P.L. Crispen, 2009	154	71	Any	2.4	31	0.28	26% without trend towards growth
J.C. Rosales, 2010	212	71	–	2.8 (0.5–13.7)	35	0.34	0.29–2.3
R.J. Mason, 2011	82	74	–	2.3 (0.8–5.4)	36	0.25	<2.45 cm—0.13 cm/year >2.45 cm—0.40 cm/year
M.A.S. Jewett, 2011	178	73	–	2.1 (0.4–4)	–	0.13	0.14 cm/year—Malignant 0.17 cm/year—Benign

than 4 cm; aggressive growth of the tumor (tumor doubling for the period less than 12 months) was verified in 12 patients (6.7%), and metastases appeared in 2 patients (1.1%). In the opinion of the authors of this study, rapid progression or the appearance of distant metastases is rather rare during the first two years of active observation even in patients with histologically confirmed RCC, which allows the recommendation of active monitoring of elderly patients and patients with severe concomitant pathology (Table 5) [22].

The obtained research results served as the basis for the introduction and use of active observation tactics, which are acceptable for strictly selected patients, namely, for elderly patients and patients with severe concomitant pathology. These studies once again give grounds to consider the appropriateness of diagnostic oncological screenings in elderly people. While routine dispensary procedures (ultrasound, mammography, fluorography, etc.) in younger patients allow the timely detection of a possible oncological pathology, this can only be additional stress for an elderly person. An example is the situation with active and mass screening of prostate cancer via the determination of prostate specific antigen (PSA). This method does not always indicate the presence of a malignant tumor, but, if it nevertheless exists, then it is impossible to establish the degree of its aggression or to determine the treatment tactics without an additional thorough examination. The hyperdiagnostics of prostate cancer has led to extremely high surgical activity, including in elderly patients, for whom surgical treatment by and large has not lead to anything other than a significant decrease in the quality of life. One cannot but mention the economic issue. Recent estimates in North America report that approximately 45% of U.S. health insurance is spent on preventive and often unreasonable examinations. We are talking about the costs of mass screening programs for the detection of malignant tumors in elderly people.

At present, there are still no specific instrumental or molecular indicators that could reliably predict the

progression of the tumor process. Dynamic monitoring is recommended every three months during the first year (ultrasound or CT). Subsequently, the observation frequency can be reduced. If the tumor rapidly grows in size or if its size reaches 4 cm or more in diameter, it is recommended that the possibility of surgical treatment once again be considered. It is not advisable to recommend active observation tactics to young patients without concomitant severe pathology. The safety and relevance of long-term active observation is still a topic of discussion. One cannot but note the general increase in oncologists' awareness of the consequences of radical surgery in case of kidney tumors, which are often associated with a higher risk of the development of chronic renal failure, cardiovascular disorders, and an increased risk of early death. While Western clinical recommendations describe the tactics of active observation with great understanding, this issue is still extremely poorly covered in Russia. Along with improvement of the material and technical basis and the emergence of new approaches to treatment, personification in oncological practice is becoming increasingly important. An individual approach to each patient must include all aspects related to the upcoming treatment of the revealed pathology, including the diagnostic and deontological aspects. Elementary logic, understanding, and dialogue can largely affect the duration and quality of life in a particular patient. Therefore, the tactics of active observation can be applied only when the doctor and patient are aware of the possible risks of a particular treatment option and can calculate them.

CONCLUSIONS

The availability and improvement of diagnostic techniques has resulted in a steady increase in the percentage of accidentally detected, clinically insignificant, small kidney tumors in elderly patients over the age of 65–75.

Since surgery is used as the main treatment method for kidney tumors, it is important to make a correct and careful consideration in the decision to perform surgery for elderly patients, because the risk of surgical intervention often may be more significant than the risk of tumor progression.

Oncologists in the United States and Europe are increasingly inclined towards the choice of less aggressive approaches in the treatment of elderly patients. The results of studies indicate the objectivity of these views.

Target studies on active observation have not been conducted in Russia; there are insufficient data on the use of this method in the real conditions of our country, as a result of which no clear clinical recommendations based on a personalized approach to the elderly have been formed to date.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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Translated by L. Solovyova