METASTATIC LESION OF THE SPINE DUE TO RENAL CELL CARCINOMA: OUTCOMES AND SURVIVAL AFTER TUMOR RESECTION

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Objective. To evaluate the impact of surgical intervention and targeted therapy on the results of treatment and survival of patients with metastases of renal cell carcinoma to the spine.
Material and Methods. Retrospective analysis of 100 patients (76 men, 24 women, mean age 58.4 years) with renal cell carcinoma metastases to the spine was carried out. Metastasectomy (en block resection) was performed in 39 patients, palliative decompression and stabilization — in 61. Twenty six patients received adjuvant targeted therapy (7 with metastasectomy, 19 with palliative decompression). The pain syndrome (VAS), neurological status (Frankel scale), and survival time (from the moment of surgery till the lethal outcome or the last follow-up examination) were assessed. The Kaplan — Meier survival analysis and Log-rank test were performed. A p-value < 0.05 was considered significant.
Results. All patients demonstrated restoration of neurologic function and reduction of pain syndrome. There was no significant difference in survival time in patients with metastasectomy and palliative decompression ($p = 0.47$). Statistically significant survival benefit was observed in patients who underwent targeted therapy ($p = 0.0019$).
Conclusion. Targeted therapy increases survival time in patients with renal cell carcinoma metastases to the spine. Metastasectomy is advisable with additional targeted therapy.
Key Words: spine, metastasis, tumor, renal cell carcinoma, survival.

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In Russia in 2015, a total of 150 016 patients were registered in oncological hospitals [3]. Based on autopsy data, at least 70 % of patients with cancer have spinal metastases [6]. Metastatic lesions to the spine in 10 % of patients are clinically manifested with spinal cord compression and spinal column instability [9]. Despite reports on the efficacy of modern targeted therapy [14], the prognosis for patients with renal cell carcinoma metastases (RCCMs) to the spine remains poor [2, 8, 13]. According to Jung et al. [10], five-year survival in patients with spinal metastases comprises 9 % compared to 30 % survival for patients who have metastases at other osseous sites.

Approaches to surgical treatment of RCCMs differ for multiple and solitary lesions. In multiple metastases, surgery is aimed at spinal column stabilization and decompression of neural structures from tumor masses [4, 7]. Meanwhile, in solitary metastatic lesions to the spine, the surgery includes complete resection of the metastasis, according to oncological principles of ablastic tumor resection [5, 12]. The long-term outcomes after such surgical interventions taking into account the impact of systemic therapy attract clinical interest.

The aim of this study is to assess the influence of the type of surgery and targeted therapy on the treatment outcomes for patients with RCCMs.

Material and Methods

A retrospective study of 100 patients treated in 2003–2014 has been performed.

The inclusion criteria were metastases to the spine due to renal cell carcinoma, data on the outcomes of the disease.

The exclusion criteria: minimally invasive procedures (vertebroplasty and others), impossible surgical treatment (ECOG performance status >4).

According to these criteria, the study included 24 (24.0 %) women and 76 (76.0 %) men. The age ranged from 32 to 79 years (the median age was 58 years).

Patients underwent two types of surgical treatment:

1) conditionally radical reconstructive and restorative surgery (metastasec-

tomy) that included total resection of the tumor (when possible the tumors were removed as asingle block (en block resection)), an interbody implant insertion into the resulting vertebral body void and instrumental spinal stabilization. This type of operation was used in 39 patients with solitary RCCMs and the removal of the primary tumor. Only posterior approach was utilized for the thoracic spine; anterior and posterior approaches were employed for the cervical and lumbar spine;

2) palliative decompression and stabilization, which included intralesional tumor excision, resection of the posterior vertebral structures (arches, articular processes, vertebral pedicles) and soft-tissue component of the tumor, compressed neural structures, and instrumental stabilization of the vertebral column. This type of surgery (decompressive laminectomy) was applied to 61 patients primarily with multiple bone metastases of renal cell carcinoma or visceral metastases, severe neurological disorders or rapid progression of the disease.

The information on the estimated demographic parameters was taken from the patients' medical records. Pain syndrome was assessed using 10-score VAS scale pre- and postoperatively. Neurological status was evaluated using the Frankel grade. The cases which required specific treatment were regarded as complications. Survival was assessed from the moment of surgery till the lethal outcome or the last follow-up examination.

Statistical analysis was performed using the Statistica 10.0 software package and the R3.3.2 software environment [17]. Sampling distribution was evaluated using the Shapiro – Wilk test. The equality of means between two samples was checked with Student's t-test in normal distribution; Mann–Whitney U-test was used for non-normal distribution. Discrete variables were verified using the Fisher's two-tailed exact test. The Kaplan–Meier analysis was performed to estimate survival of all patients. Log-rank (Mantel-Cox test) was used to assess survival between different groups. A p value < 0.05 was considered significant.

Results

Metastases to the thoracic spine were revealed in 48 (48 %) patients, to the lumbar spine – in 32 (32 %), to the thoracic and lumbar spine – in 14 (14 %), to the lumbar and sacral spine – in 4 (4 %), to the cervical and thoracic spine – in 1 (1 %), and to the cervical and lumbar spine – in 1 (1 %).

According to medical record data, nephrectomy was performed in both groups in 87 % of patients. Synchronous metastases (diagnosed at the same time or within the first 6 months following diagnosis of renal cell carcinoma) were observed in 66 % of patients, metachronous (revealed more than 6 months after diagnosis of renal cell carcinoma) – in 34 %.

Solitary RCCMs to the spine were detected in 8 (8 %) patients, multiple bone metastases – in 42 (42 %); concomitant with metastases into internal organs – 50 (50 %), including metastatic lesions to the lung – 33 (33 %), to the brain and liver – in 2 (2 %; Table 1). The number of metastases and the periods of their detection did not differ significantly between groups of patients who underwent conditionally radical and palliative operations. The frequency of nephrectomy in history was similar in these groups.

The overall survival of patients with metastasectomy and decompression was analyzed using the Kaplan – Meier method. The data are presented in Fig. 1. Despite that a higher predictive survival time of patients in the metastasectomy group, there was no significant difference. The Log-rank test revealed no significant differences between the two types of surgeries. Additionally, the overall survival was studied in patients receiving targeted therapy and without (kinase inhibitors; Table 2). There were significant differences in survival time between these groups of patients (Fig. 2). The first-line targeted therapy was administered to 26 patients, the second-line – 17 (65.4 % of treated with targeted drugs), the third-line – 9 (34.6 %), the fourth-line – 2 (7.7 %), and the fifth-line and sixth-line targeted therapies – 1 in each (3.8 %).

Postoperative pain syndrome on VAS scale regressed from 7.1 (95 % CI from 6.7 to 7.4) to 2.6 (95 % CI 2.3 to 2.8) scores; the differences were significant ($p < 0.0001$). Neurological function showed a positive dynamics after surgical treatment. The proportion of patients who were unable to walk (Frankel A, B, C) decreased ($p = 0.059$) compared to patients who retained their walking ability (Frankel D and E; Fig. 3).

Therefore, neurological deficit and pain regressed postoperatively in both groups.

A total of 51 complications were observed in 43 patients (Table 3). The third of complications (29.4 %) was associated with instrumental fixation of the affected part of the spine. Temporary neurological deficits were noted in 3 (5.9 %) patients and wound complications – in 15 (29.4 %). Deep infection was the most frequent reason of reoperations. Somatic complications were revealed in 3 patients; local tumor relapse – in 13; there was no significant difference between the groups with different types of surgery ($p = 0.241$) and between patients with targeted therapy and without ($p = 0.504$).

Discussion

The preservation of spinal stability and intactness of nerve structures are some of the most essential factors that contribute to improved quality of life in limited life span of patients with spinal metastases [18]. Since metastases cause aggressive lytic bone lesions, represent hypervascular and radioresistant formations, treatment of patients with RCCMs is demanding. Our study confirms a positive clinical outcome of surgical spinal stabilization and decompression of neural structures in RCCMs.

There are several published papers that address the influence of surgical treatment on survival time in RCCMs. Jackson et al. [9] reported on the average survival of 14.1 months following various decompressive procedures. Prabhu et al. [15] showed that survival time averaged 11.5 months (8.7–21.4 months) in 37 % of patients after operation. Qurai-

Table 1
Characterization of patients in groups with metastasectomy and decompression

Parameters	Total (n = 100)	Metastasectomy (n = 39)	Decompression (n = 61)	P
Gender, n				
male	76	32	44	0.3389
female	24	7	17	
Age, years (SD	58.4 (11.6)	60.6 (9.4)	57.7 (12.3)	0.186
*Number of levels, n***				
1	75	35	40	0.0085*
2	22	2	20	
3	3	2	1	
Neurological status, n				
Frankel A, B, C	50	2	52	<0.0001*
Frankel D, E	50	37	13	
Tokuhashi scale, scores (SD)	11.1 (2.4)	12.3 (1.7)	10.4 (2.5)	0.0001*
SINS scale, scores (SD)	11.2 (2.2)	9.4 (1.3)	12.1 (2)	<0.0001*
Metastases, n				
synchronous	66	28	38	0.390
solitary	8	4	4	0.708
concomitant with metastases into internal organs	50	13	36	0.015*
Nephrectomy in anamnesis, n	87	36	51	0.710
Target therapy, n	26	7	19	0.167

SD — standard deviation, *significant differences, **patients with lesions at two or more levels are combined into one subgroup for comparison.

shi et al. [16] reported the mean survival of 12.3 months. The advances in surgical techniques of spinal reconstruction have led to a paradigm shift towards conditionally radical surgery with complete tumor removal [1, 19]. A paper by Kato et al. [11] analyzes the outcomes after en block resections of RCCMs and the mean survival was shown to be 130 months. However, according to our data, the survival of patients, who underwent metastasectomy, differed insignificantly from the survival of patients after palliative decompressive surgery. In our study, adjuvant targeted therapy was a more important factor affecting survival. A high level of significance was revealed in an analysis of groups undergoing different treatments and thus the results of multiple comparisons can be neglected. We concluded that patients who received targeted therapy lived longer, regardless of the type of operation. Nevertheless, this statement is not in contrast with the conclusions of previous studies, where

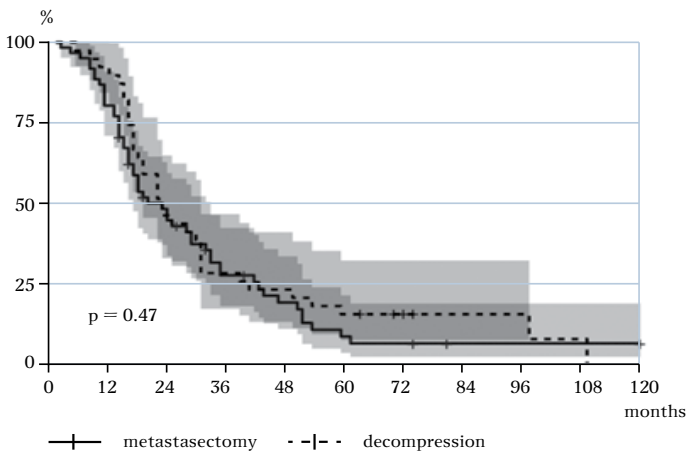

Fig. 1
Survival time of patients after surgery: the median survival time in patients with metastasectomy (n = 39 – 22 months (95 % CI 18–30), decompression (n = 61 – 19 months (95 % CI 16–32); Log-rank test p = 0.47

Table 2
Characterization of patients in groups with targeted therapy and without

Parameters	Total (n = 100)	Targeted therapy (n = 26)	Without targeted therapy (n = 74)	P
Gender, n				
male	76	20	56	1.000
female	24	6	18	
Age, years (SD)	58.4 (11.6)	57.1 (11.5)	59.8 (13.4)	0.329
*Number of levels, n***				
1	75	15	57	0.027*
2	22	11	11	
3	3	0	3	
Neurological status, n				
Frankel A, B, C	50	3	47	<0.0001*
Frankel D, E	50	23	27	
SINS scale, scores (SD)	11.2 (2.2)	11.3 (2.3)	10.9 (2.2)	0.458
Tokuhashi scale, scores (SD)	11.1 (2.4)	11.1 (2.3)	11.6 (2.3)	0.328
Metastases, n				
synchronous	66	11	55	0.004*
solitary	8	2	6	1.000
multiple bone metastases	42	13	29	0.364
concomitant with metastases into internal organs	50	13	37	1.000
Nephrectomy in anamnesis, n	87	24	63	0.505
Metastasectomy, n	39	7	32	0.167

SD — standard deviation, *significant differences, **patients with lesions at two or more levels are combined into one subgroup for comparison.

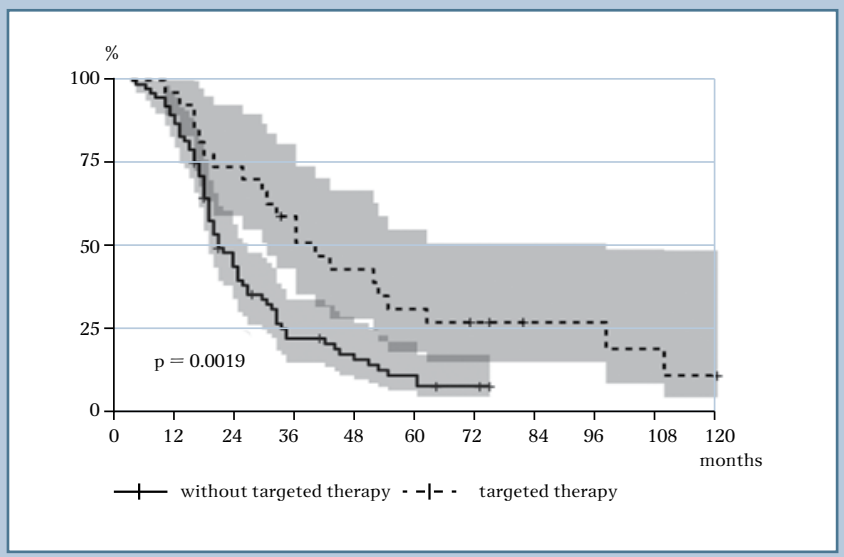

Fig. 2
Postoperative survival time of patients: the median survival time of patients who were administered targeted therapy (n = 26) – 34 months (95 % CI 27–61), without targeted therapy (n = 74) – 18 months (95 % CI 16–23); Log-rank test p = 0.0019

most patients underwent targeted therapy after spinal surgery. Our data support the importance of complex treatment of RCCMs with consistency of procedures performed by health professionals.

This study had several limitations. During the 11-year period of material collection, treatment protocols for patients with renal cell carcinoma were changed repeatedly and hence targeted therapy included different kinase inhibitors in various periods (avastin combined with roferon, nexavar, sutent, pazopanib, tivozanib, torisel, afinitor). For this reason, it was impossible to assess the impact of various combinations of systemic therapy on patient survival. Due to the small number of patients (n = 7) who received targeted therapy, we did not perform a comparative analysis of patients depending on the treatment received within the metastasectomy group.

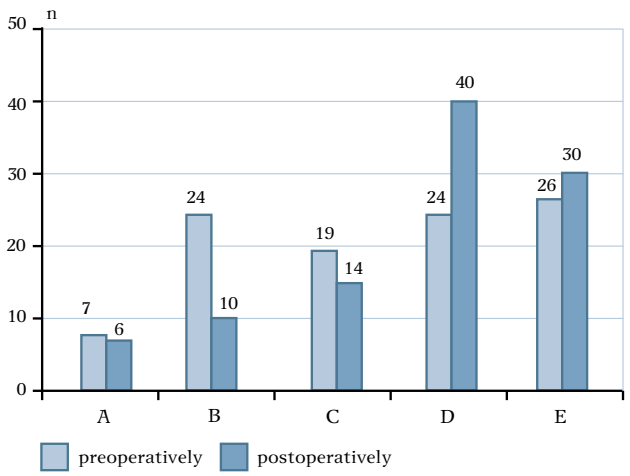

Fig. 3
Neurological status according to Frankel grade in patients before and after surgery

Table 3
Postoperative complications in groups of patients

Parameters	Metastasectomy (n = 39)	Decompression (n = 61)
Complications in total	22	29
Implant instability	1	1
Implant fracture	1	0
Degenerative changes in adjacent segments	5	7
Paresis after surgery	2	2
Impaired sensitivity	1	0
Deep wound infection	2	5
Postoperative hematoma	3	2
Liquorrhea	2	1
Pneumonia	2	0
Pulmonary thromboembolism	0	1
Local tumor relapse	3	10

P = 0.418.

Conclusion

Surgical treatment of patients with RCCMs to the spine demonstrated positive outcomes. Complete removal of metastases is advisable, if targeted therapy of renal cell carcinoma is planned.

This study is not a sponsored project. The authors declare that they have no conflict of interest.

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