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Simultaneous or staged surgery in patients with kidney tumors and concomitant cardiac disease

Uladzimir Andrushchuk[1], Yury Ostrovsky[1], Sergey Krasny[2], Sergey Polyakov[2], Vladimir Zharkov[3], Alexander Rolevich[2], Svetlana Kurganovich[1], Valery Krutau[1], Siarhei G. Amelchanka[1]

[1]Republican Scientific and Practical Centre 'Cardiology', Department of Cardiac Surgery, Minsk, Belarus
[2]N.N. Alexandrov National Cancer Centre, Department of Urology, Minsk, Belarus
[3]N.N. Alexandrov National Cancer Centre, Department of Thoracic Medicine, Minsk, Belarus

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Corresponding author
Uladzimir Andrushchuk
Republican Scientific and Practical Centre 'Cardiology'
Department of Cardiac Surgery
39-52, Kahovskaja Street
220068 Minsk, Belarus
heartslight@mail.ru

Introduction To evaluate outcomes of simultaneous and staged surgery in patients with kidney tumors and concomitant cardiac disease.

Material and methods Between October 2001 and October 2015, fifteen patients (Group 1) underwent simultaneous surgery and fourteen patients (Group 2) underwent staged surgery. 89.7% were males (26/29), and the mean age was 60.8 ±1.16 years. Locally advanced cancers (Stage III) were registered in the two groups in 11 vs. 3 patients (p = 0.016) and localized (Stage I) disease in 2 vs. 10 (p = 0.007), respectively. 18 patients (62%) were operated for coronary heart disease, while 10 patients (35%) underwent surgery for valvular heart disease. Nephrectomy was performed in 14rs 5 patients respectively (p = 0.003) while partial nephrectomy in 1rs 7 patients (p = 0.005).

Results In the two groups, the 30-day mortality was 13% (2 cases) and 7% (1 case), p = 1.0, and major hospital complications were observed in 3 (20%) and 2 (14%) cases, respectively, p = 0.53. The median follow-up in Group 1 and Group 2 was 87 months (range, 23.3 to 146.8 months) and 39 months (range, 3.9 to 98 months), respectively, p = 0.001. Three-year overall survival was 73.3 ±11.4% (95% CI 50.5–96.1) and 77.9 ±11.3%, respectively, p = 0.70, and three-year disease-free survival was 83.9 ±10.4% and 75.0 ±21.7%, respectively, p = 0.91.

Conclusions Simultaneous and staged surgery for kidney tumors and concomitant cardiac disease are feasible procedures. Patients with advanced tumors and complicated disease course can benefit from early intervention and consequently a simultaneous approach can be a preferred option for them. For localized renal tumors, staged surgery should be used.

Key Words: kidney tumors ‹› coronary heart disease ‹› valvular heart disease ‹› surgical treatment

INTRODUCTION

Surgery is the most effective strategy for the majority of patients with kidney cancer. Pre-existing severe cardiac disease, however, may significantly alter a patient's ability to undergo surgery [1, 2, 3]. Myocardial revascularization in patients with coronary heart disease (CHD) and surgical correction of valvular heart disease (VHD) result in reduced risk of perioperative cardiovascular complications during subsequent surgical intervention for extracardiac cancer and potentially improve long-term survival [4–7].

Surgical procedures for cardiac disease and kidney tumors can be performed in stages and at the same time (simultaneously). The first experience of simultaneous surgical treatment in patients with extracardiac cancers and cardiac disease was reported by Dalton et al. in 1978 [8]. Traditionally, these patients undergo surgery in stages. However, the increased cost of staged treatment [9] and immunosuppressive

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effect of cardiopulmonary bypass, which might be associated with cancer progression [10], have aroused significant interest in simultaneous surgical treatment [6, 11, 12, 13]. Moreover, there are only few reports in the literature on individual cases of simultaneous and staged surgery in patients with kidney cancer and concomitant cardiac disease.

The purpose of this study was to evaluate early and long-term outcomes of simultaneous and staged surgery in patients with kidney tumors and concomitant cardiac disease.

MATERIAL AND METHODS

Patients

There was a prospective non-randomized cohort study of 29 patients who were admitted to the National Cancer Centre between October 2001 and October 2015. The inclusion criteria were clinically malignant renal masses according to contrast-enhanced computed tomography, surgically resectable tumor, presence of significant cardiovascular disease (CHD, VHD, mixoma) associated with increased risk during a cancer surgery, with indication for surgical correction. Exclusion criteria were contraindications to intervention in heart or kidneys, life expectancy of less than 1 year and presence of metastases detected by preoperative imaging.

The interdisciplinary team defined indications for simultaneous or staged surgery. A simultaneous approach was generally preferred in patients with locally advanced tumors and patients with localized disease who underwent staged surgery. Preoperative patient examination included computed tomography of chest, abdomen and pelvis, cardiac ultrasound and coronary angiography [14, 15, 16]. Fifteen patients underwent simultaneous surgery (Group 1) and fourteen patients were managed via a staged approach (Group 2). The study was approved by the ethic committees of each center, and all the participants signed informed consent forms.

Surgery

Median sternotomy was used for cardiac surgery (CS) in simultaneous and staged procedures. Renal surgery (RS) in Group 1 was performed through a second incision made immediately after inactivation of heparin with protamine and closure of sternotomy. RS in staged procedures was undertaken after some rehabilitation period, the duration of which was defined by the interdisciplinary team. For those patients, the time between discharge from the cardiac center and admission to the cancer center was considered as an interstage period. Simultaneous operations were carried out jointly by cardiac and urologic surgeons in the cardiac center. Staged surgical treatment was performed separately at tertiary referral centers.

Complications and in-hospital mortality and follow-up

Major hospital complications (MHC), Clavien-Dindo Grade IIIb–V, included those that occurred during hospital stay and required another surgery or led to a serious deterioration in a patient's condition. Mortality and MHC were assessed during the first 30 days after surgery.

Follow-up examination included symptom assessment, electrocardiography, exercise stress test (in CHD), echocardiography, ultrasound scan and computed tomography of chest and abdomen. The tests were performed at 3, 6, and 12 months after intervention and every 12 months thereafter.

Statistical analysis

The primary endpoint in the study was a 30-day mortality; major hospital complications, 3-year overall survival and disease-free survival were used as secondary study endpoints. Outcomes between the two groups were compared and evaluated cumulatively to assess the efficacy of the developed approach.

Continuous variables with normal distribution were reported as the mean and standard deviation ($M \pm m$) using the Kolmogorov-Smirnov test. These values were compared with Student's t-test or repeated measures t-test. Medians and percentiles (25; 75) were used for asymmetric continuous variables. Categorical variables presented as percentages and frequencies were compared using two-sided Chi-square test and Fisher's exact test. The Wilcoxon signed-ranks test was used to compare repeated measurements.

Survival was calculated using the Kaplan-Meier method and log-rank test. A statistical hypothesis of equal distributions was rejected at $p \leq 0.05$. We used SPSS-20 software package for all statistical analyses.

RESULTS

Patient characteristics and surgical procedures

26 male and 3 female patients entered the study at a mean age of 60.8 ± 1.2 years. The two groups were comparable in terms of age and gender distribution. The primary cancer pathology was renal cell carcinoma in 27 patients and urothelial carcinoma

of the renal pelvis in 2 (both in Group 2). Localized tumors (pT1–2) were found in 3 patients (20%) in Group 1 and in 11 patients (79%) in Group 2 (p = 0.003). Other tumors were locally advanced, except one case in Group 1 with single liver metastasis that was found intraoperatively and completely resected.

Characteristics of cardiac disease and CS procedures are shown in Table 1. Overall, CHD was diagnosed in 18 patients (62%), VHD was diagnosed in 10 (35%), and one patient (4%) was diagnosed with cardiac myxoma. Coronary artery bypass grafting was performed in 18 patients (62%), and 19 patients (66%) underwent valvular correction, in particular, valve replacement (10 patients, 35%) and valve repair (9 patients, 31%). Bioprosthetic and mechanical heart valves were used in an equal number of cases – five cases each (17%). CS was performed under cardiopulmonary bypass in 26 cases (90%). There were no significant differences in the duration of CS, myocardial ischemia or cardiopulmonary bypass between the two groups.

Of a total 15 patients in Group 1, radical nephrectomy was performed in 14, including one case of inferior vena cava thrombectomy and two cases of nephroureterectomy with bladder cuff excision. One patient underwent partial nephrectomy. In Group 2, radical and partial nephrectomy was performed in 5 and 7 patients, respectively (p = 0.008); two patients had died before the cancer surgery.

The main postoperative period characteristics are presented in Table 2. Blood loss due to CS was significantly higher in Group 2 than compared to Group 1, which may result from the greater use of partial nephrectomy.

Table 1. *Characteristics of cardiac disease and interventions*

Characteristic	Group 1 (n = 15)	Group 2 (n = 14)	P-value
Coronary heart disease	9 (60%)	9 (7%)	1.0
Valvular heart disease	6 (40%)	4 (29%)	0.62
Left atrial myxoma	0	1 (7%)	1.0
NYHA FC II III IV	4 (27%) 8 (53%) 3 (20%)	4 (29%) 9 (64%) 1 (7%)	0.7
Angina FC II III IV	3 (20%) 4 (27%) 2 (13%)	2 (14%) 7 (50%) 0	0.9
Left ventricular ejection fraction, %	52.8 ±2.4	46.6 ±3.6	0.16
Aorta prosthesis	0	3 (21%)	0.10
Valve prosthesis	6 (40%)	4 (29%)	0.82
Valve repairs	2 (13%)	7 (50%)	0.39
Coronary artery bypass grafting	9 (60%)	9 (64%)	1.0
Cardiopulmonary bypass/ off-pump intervention	12 (80%) / 3 (20%)	14 (100%)	0.22
Euroscore-2	2.5 ±0.5	3.3 ±0.7	0.33

NYHA – New York Heart Association; FC – functional class

Table 2. *Main postoperative characteristics in study groups*

Characteristic	Group 1 (n = 15)	Group 2 (n = 14)	P-value
Duration of ventilation support after operation, min	230 ±60	258 ±32	0.69
Duration of inotropic support after operation, hours	0.3 ±0.2	2.9 ±2.3	0.17
Stay in intensive care unit, days	0.8 (0.5; 1.5)	1.8 (0.9; 2.5)	0.007
Blood loss during operation, ml	400 (350; 500)	465 (400; 662)	0.58
Blood loss after operation, ml	350 (220; 550)	435 (357; 525)	0.17
Total blood loss, ml	600 (750; 1250)	950 (798; 1108)	0.56
Blood loss during and after CS, ml	510 (420; 680)	640 (450; 760)	0.37
Blood loss during and after RS, ml	250 (220; 310)	440 (323; 538)	0.004
Blood transfusions	0 (0; 1.0)	0 (0; 0)	0.33

CS – cardiac surgery; RS – renal surgery

Morbidity and mortality

There were five cases of major hospital complications within 30 days of surgery: three cases (20%) in Group 1 and two cases (14%) in Group 2. One patient (7%) in Group 1 died suddenly of ventricular fibrillation (VF) on Day 10 after double valve repair and a left nephrectomy. Two patients in Group 1 (13%) suffered postoperative bleeding which one patient died of. In Group 2, spinal stroke occurred in one patient (7%) and low cardiac output syndrome developed in another one (7%), which resulted in that patient's death the day after coronary artery bypass grafting with double valve repair and left ventricular aneurysmoplasty. Overall, 2 (14%) and 1 (7%) patients died within 30 days after surgery in Groups 1 and 2, respectively. There were no cases of 30-day mortality after renal surgery among Group 2 patients.

Interstage period in Group 2

During the interstage period one patient (1/14, 7%) died of spinal stroke after triple valve correction and subsequent abdominal aorta replacement. The median interstage period was 110 days (48; 169). Six (6/14, 43%), ten (10/14, 71%), and eleven patients (11/14, 79%) underwent RS within 3, 6, and

9 months after CS, respectively. Only one patient (7%) was operated on almost three years later (due to the patient's unwillingness).

Follow-up

Thirteen out of 15 (87%) patients in the first group and 12 out of 14 (86%) patients in the second group were followed from 4 to 146 months. The median follow-up of 87 months (range, 23 to 147 months) was longer in Group 1 compared to 39 months (range, 4 to 98 months) in Group 2, p = 0.001.
The main follow-up results are shown in Table 3. In the follow-up period exertional angina functional class (Figure 1) and New York Heart Association functional class (Figure 2) in the two groups were significantly lower compared to the baseline. Overall mortality in both groups was 5 patients (5/29, 17.2%). No statistical differences in cardiac and tumor progression-related mortality were found between Groups 1 and 2, (p = 1.0). Tumor progression was observed in four patients in the two groups (4/29, 13.8%), including one patient (1/29, 4%) after off-pump coronary artery bypass graft surgery (p = 1.0). Two patients (2/29, 7%) were surgically treated for local recurrence and are still alive. A cardioembolic stroke due to noncompliance with anticoagulant therapy 24 months after simultaneous nephrectomy and triple valve correction (mechanical mitral and aortic prostheses) was a cardiac cause of death in one patient (1/15, 7%) in Group 1. Another patient (1/15, 7%) in the first group underwent coronary stenting for unstable angina 16 months after aortic valve replacement. 3-year overall survival for total cohort was 74.5% (95% CI 48–87%), and 3-year disease-free survival was 83% (95% CI 66–100%) (Figure 3).

Table 3. *Main parameters of long-term follow-up period in study groups*

Parameter	Group 1 (n = 15)	Group 2 (n = 14)	P-value
NYHA FC I	6 (40%)	9 (64%)	
II	6 (40%)	2 (14%)	0.09
III	1 (7%)	0	
CCS FC I	3 (20%)	0	
II	2 (13%)	2 (14%)	0.23
III	1 (7%)	0	
Tumor progression	3 (20%)	1 (7%)	0.59
Mortality from tumor progression	2 (13%)	0	0.48
Mortality from cardiac causes	1 (7%)	0	1.0
Unknown cause of death	1 (7%)	1 (7%)	1.0
Overall long-term mortality	4 (27%)	1 (7%)	0.33
3-year overall survival, %	73.3 (95% CI 50.5–96.1)	77.9 (95% CI 55.8–100)	0.70
3-year disease-free survival, %	83.9 (95% CI 63.5–100)	75.0 (95% CI 32.5–100)	0.91

CCS – Canadian Cardiovascular Society; FC – functional class; NYHA – New York Heart Association

DISCUSSION

Cancer patients at high risks of perioperative cardiac complications and mortality are recommended to undergo CS before definitive oncological therapy [14–18]. Published reports of surgery in patients with kidney malignancies and concomitant cardiac disease include experiences with 6 to 9 cases [12, 6] and isolated cases of cardiac interventions in patients with renal cell carcinoma and caval tumor thrombus [19, 20]. To our knowledge, we present the largest series of cases of simultaneous (15 cases) and staged (14 cases) surgery for renal tumors and concomitant cardiac disease.
Both treatment approaches have their own advantages and disadvantages, and corresponding indications based on tumor stage and concomitant cardiac disease severity. Patients with advanced tumors can benefit from early intervention and consequently a simultaneous approach can be a preferred option. Gross hematuria and massive tumor invasion of the inferior vena cava also make simultaneous surgery more preferable. Exceptions can be patients with low functional reserves (myocardial, respiratory, kidney etc). For localized renal tumors, both approaches are feasible and we routinely perform staged surgery.
We are convinced that both approaches do not affect intervention efficacy (use of LIMA-graft, etc.), at least, in cases with good life expectancy. However, we used biological prostheses to reduce prosthetic or warfarin-induced complication risks during RS where staged surgery was performed. CS was always done first and after inactivation of heparin with protamine patients underwent RS. That strategy allowed us to reduce risks of cardiac complications and perioperative bleeding at simultaneous approach and perform nephron-sparing surgery where indicated. Our algorithm enabled us to perform surgery with acceptable MHC (17%) and mortality (10%) rates with no significant differences in the two groups.
According to several international recommendations [14, 15, 16], the interstage period for patients with noncardiac disease should be around six months. We believe that the interstage period in the absence of MHC after CS for patients with kidney tumors should not exceed three months, thus reducing the

risk of tumor progression. Neither MHC nor hospital mortality was recorded among the Group 2 patients who underwent RS within the first three months after CS (6/12, 50%). Tourmousoglou et al. [14] also reported that such period for patients with lung cancer and concomitant CHD should be shortened (3 to 6 weeks). We also recognize certain advantages of simultaneous interventions with concomitant off-pump coronary artery bypass grafting [21, 22, 23], but our series included only three patients (3/18, 17%) operated off-pump and we are not certain if cardiopulmonary bypass is associated with tumor progression.

The favorable results with respect to overall and diseases-free survival and long-term cardiac mortality in patients in the two groups also confirm the feasibility of both strategies. As we found, long-term survival in patients with lung cancer and CHD after simultaneous and staged treatments correlates with cancer stage and does not depend on cardiac disease severity [13]. An insufficient number of observations in our study probably did not allow us to reach the same conclusions regarding the dominance of cancer-related causes of deaths over cardiac causes. Staged and simultaneous surgical procedures were effective in reducing angina or heart failure functional class, which improved the quality of life in patients with cardiac disease.

Our study has some limitations that preclude a proper comparison of the outcomes in the study groups. The small sample size, lack of randomization and significant differences between the two groups in tumor stage, renal surgery type, and follow-up period make it impossible to decide on a preferred option. Despite being the largest reported series, this comparison is largely underpowered and we cannot rule out that larger number of patients would present statistically significant differences in survival.

CONCLUSIONS

Simultaneous and staged surgery in patients with kidney tumors and concomitant cardiac disease are feasible procedures with acceptable mortality and major complications rates and good overall and disease- free survival. Patients with advanced tumors and complicated course of disease (e.g. gross hematuria or tumor invasion of inferior vena cava) can benefit from early intervention and consequently a simultaneous approach can be a preferred option for them. Staged surgery should be used for localized renal tumors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

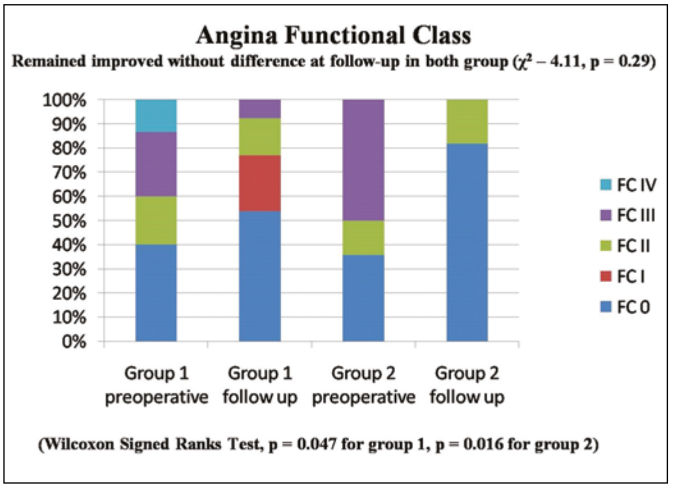

Figure 1. *Change of angina FC in Group 1 and Group 2 (FC – functional class).*

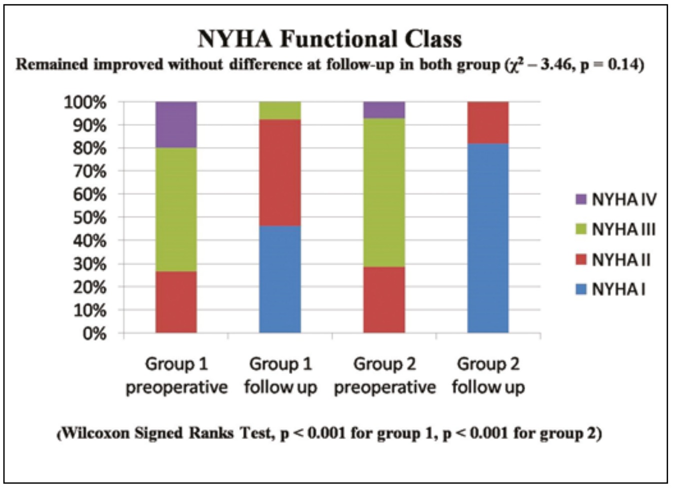

Figure 2. *Change of NYHA functional class in Group 1 and Group 2 (NYHA – New York Heart Association).*

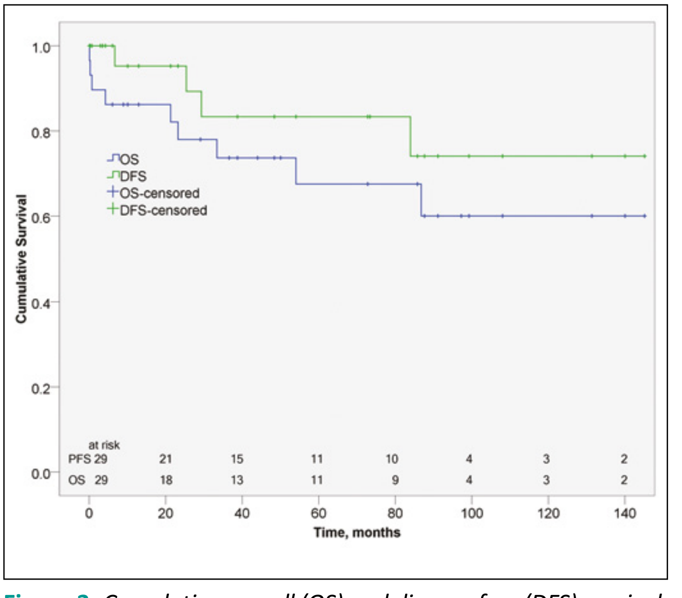

Figure 3. *Cumulative overall (OS) and disease-free (DFS) survival.*

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