

Original article



ADRENALECTOMY FOR ISOLATED METASTASES

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ABSTRACT

Background: Isolated adrenal gland metastases are not frequently finding. The aim of the present retrospective study was to estimate clinical and pathological parameters that could be used to predict survival after adrenalectomy.

Material and methods: A total of 34 patients with adrenal gland masses suspected to be metastases was included in this study. The group of patients with isolated metastases was 19 (56%) and a group of patients with adrenal adenomas - 15 (44%).

Results: The sample of patients consisted of 18 (53%) men and 16 (47%) women from 40 to 81 years old with a mean (\pm SD) age of 61.6 ± 10.3 years, presented with adrenal mass suspected to be metastases. Nineteen (56%) of them had demonstrated metastases and 16 (84%) metachronous with median overall survival (OS) 54.6 (range 43-66) months. Median OS in the group with metastases was 22.6 months. Lung carcinoma was the most common primary tumour metastasizing in the adrenal gland - 58% of all metastases with a disease-free interval (DFI) of 13 months. It was presented by shorter median survival than the rest primary tumour types (37.8 vs. 96.7 months; log-rank test, $p=0.028$). In the multivariate Cox's hazard analysis of the surgical technique was found to be an independent prognostic factor ($p=0.047$), together with lung carcinoma vs. renal cell carcinoma ($p=0.045$).

Conclusion: Adrenalectomy due to isolated metastases in the adrenal glands showed the median overall survival of 22.6 months. Shorter survival periods were associated with lung carcinoma, $DFI < 12$ months, conversion to open surgery, synchronous metastases, but not with age, tumour size or resection status.

Keywords: adrenal gland, adrenal metastases, adrenalectomy, laparoscopic adrenalectomy.

INTRODUCTION

A series of primary malignant diseases can metastasize into the adrenal glands [1, 2]. According to some authors, the abundant sinusoidal blood flow and the nu-

merous arterial perfusion pathways contribute to the high incidence of metastatic implantation [2]. Metastasis in the adrenal gland have been reported in autopsy in 27-38% of patients with known extra-adrenal malignancy [1, 3, 4], but isolated metastases have been established in less than 1% of those cases [4]. Lung, kidney, and bowel carcinoma, melanoma and breast cancer most often metastasize into the adrenal glands [5-8].

An adrenal metastasis is usually limited to the adrenal gland, which provides better chances for its total removal [6, 9, 10]. Long-term survival rates have been reported in patients after adrenalectomy due to metastatic disease, provided there was an isolated metastasis [3, 11-13]. In terms of surgical approach, numerous authors have reported safety and similar oncological results of laparoscopic adrenalectomy for metastases compared to open surgery [11, 12, 14-16]. In the present study, we have presented our clinical results from the endoscopic removal of suspected adrenal metastases, and have tried to evaluate the significance of certain clinical and pathological parameters for prediction of long-term survival after adrenalectomy.

MATERIAL AND METHODS

We performed a retrospective study involving 34 patients, operated by various malignancies with a tumour in the adrenal gland, for the period from January 2005 to May 2015 in the Clinic of Surgery of the University Hospital "Aleksandrovska". Data was collected using medical documents. The selection of the adrenal tumours was carried out by means of computed tomography (CT) to 26 (76%) of the patients, where the density of tumour was compared to the density of water, adopted as 0 HU (Hounsfield units). Adrenal metastases with $HU > 18$ were detected in 11 (43%) of these 26 patients, and adrenal adenomas with limit values between 10 and 16 HU were noted in 15 (57%), which cannot exclude malignancy. Three (9%) patients with demonstrated adrenal metastases T2-series of the magnetic resonance imaging (MRI) showed heterogeneity and hyperintensity without any loss of signal intensity. Metastases were established in the rest 5 (15%) patients by using positron-

emission tomography (PET) with a ratio of the standardised uptake values (SUV) adrenal gland/liver > 1, which is a common criterion for differentiation between malignant and benign lesions. Overall survival (OS) was defined as the time interval from the date of adrenalectomy to the date of follow-up (01. 11. 2015) or death. Disease-free interval (DFI) was defined as the interval between the primary resection and the recognition of an adrenal mass. All of 34 patients underwent adrenalectomy. Nineteen (56%) had synchronous (≤ 6 months post resection) or metachronous (> 6 months post resection) metastases, demonstrated histologically. These are solitary lesions, such as adrenal gland is the only and first site of metastasizing. With R0 we marked the cases of complete macroscopic and microscopic resection as a final histological result, and with R1 – complete macroscopic resection with positive resection lines.

Cumulative survival curves were drawn by the Kaplan-Meier method and the differences between the curves were analysed by Mantel-Cox (long-rank) test. The Cox's proportional hazard model was used for the multivariate analysis performed with the factors that were statistically significant in the univariate analysis. Statistical significance was accepted at $p < 0.05$.

All data for this study were analysed using the IBM SPSS v 24.0.

RESULTS

In total, 34 patients with adrenal metastases 18(53%) men and 16(47%) women were studied in this group. The mean (\pm SD) age of the patients was 61.6 ± 10.3 (range 40-81) years. (Adrenalectomy was performed to all 34 patients with adrenal tumour mass; in 24 (71%) – retroperitoneal endoscopic adrenalectomy (REA) with a lateral approach, and in 10 (29%) – conversion to open surgery. Reasons for

converting to open adrenalectomy are the big size of the tumour or adhesions to the vena cava and the superior pole of the kidney. Median surgery time of the endoscopic procedures was 85 (range 60-120) min, with median intraoperative blood loss of 80 (0-300)ml. No intra- or post-operative complications were observed. The average hospital stay after endoscopic adrenalectomy was 4 days, and after conversion – 11 days. No port-site metastases or surgical lethality was recorded. The main cause of death was a progression of the primary disease. Median tumour size was estimated as 39 (12-100) mm. Left-sided localisation was observed in 20(59%) patients, and right-sided – in 14 (41%). The most common primary tumour was lung carcinoma – 15(44%), followed by breast cancer – 7 (21%), renal-cell carcinoma – 3 (9%), and carcinoma of the rectum – 3 (9%), sigmoid colon – 2 (6%), urinary bladder – 1 (3%), endometrium – 1 (3%), cervix – 2 (6%), thyroid gland – 1 (3%), malignant myeloma – 1 (3%) and seminoma – 1 (3%).

Adrenal metastases from the primary tumour were established in 19 (56%) of the patients – 16 (84%) metachronous and 3 (16%) synchronous, while in 15 (44%) there was adrenal hyperplasia or adenoma. Mean overall survival of the patients with metastasis was 25 months.

In our study, we observed a statistically significant difference between the survival of patients with metastases and their gender, since all women in the study ($n=5$) survived (log rank test; $p=0.022$) (Table 1). Median survival time in women was 65.1 (23.0-90.1) months, and in men – 42.6 (5.2-124.1) months. The factors age group (log rank test; $p=0.845$), tumour size (log rank test; $p=0.621$) and resection status R0/R1 (log rank test; $p=0.484$) were non-statistically significant (Table 2). Median survival in the group of patients with status R0 was 54.7 months, and at R1 was 49.1 months.

Table 1. Demographic data for patients with isolated adrenal metastases

Characteristic	Alive (n=8, 56%)	Dead (n=11, 44%)	p
Age(years), mean \pm SD	58.4 ± 7.9	61.7 ± 10.9	0.470
Gender (M/F)	3 (37.5%)/5 (62.5%)	11 (100%)/0 (0%)	0.005
Primary tumour			0.371
lung carcinoma	3 (37.5%)	8 (72.7%)	
renal cell carcinoma	2 (25.0%)	1 (9.1%)	
other	3 (37.5%)	2 (18.2%)	
Tumour size (mm), mean \pm SD	47.6 ± 28.3	50.5 ± 22.3	0.809
Surgical technique (conversion to open surgery/REA)	2(25%)/6(75%)	6(54.5%)/5(45.5%)	0.352
Presentation (metachronous/synchronous)	8(100%)/0 (0%)	8(72.7%)/3(27.3%)	0.228
DFI (<12month/ \geq 12month)	1(12.5%)/7(87.5%)	4(36.4%)/7(63.6%)	0.338
Resection status (R0/R1)	6(75.0%)/2(25.0%)	8(72.7%)/3(27.3%)	1.000

Table 2. Univariate and multivariate analysis of overall survival in patients with isolated adrenal metastases

Variable	Mean survival in months (95% CI)	Univariate analyses		Multivariate analyses	
		p	HR	p	HR
Surgical technique		0.025		0.047	
Conversion to open surgery (n = 8)	29(17-40)		0.244		0.079
REA (n = 11)	59(46-73)		1		1
Tumour type		0.089		0.034	
Lung carcinoma (n = 11)	38(26-50)		1		1
Renal cell carcinoma (n = 3)	78(34-122)	0.254	0.296	0.045 ^a	0.047
Other (n = 5)	97(67-126)	0.041	0.188	0.227 ^a	0.327
Disease-free interval		0.031			
Metachronous DFI<12 months (n = 3)	32(-)		0.069		
Metachronous DFI≥12 months (n =14)	59(47-71)		1		
Size of tumour		0.622		n.s.	
≤45 mm (n = 9)	55(48-62)		1		
>45 mm (n = 10)	47(32-61)		1.349		
Presentation		0.006		0.309	
Synchronous (n = 3)	24(0-55)		0.041		0.286
Metachronous (n = 16)	55(43-66)		1		1
Resection status		0.488		n.s.	
Ro (n = 14)	55(41-69)		1.604		
R1 (n = 5)	49(0-99)		1		
Age		0.846		n.s.	
≤55 (n = 7)	52(29-75)		1.131		
>55 (n = 12)	55(32-77)		0		

^a versus lung carcinoma

Statistical difference in survival between synchronous and metachronous adrenal metastasis (log rank test; $p < 0.0001$) was found. Median survival for metachronous metastases was 54.7 months, and for synchronous – 24.2 months (Fig. 1A, Table 2). By the end of the follow-up all patients with synchronous metastases were dead, while 50% of those with metachronous were still alive (Table 1). We observed the difference in the DFI in patients with various types of primary tumours and adrenal gland metastases (Table 3). The shortest survival was associated with lung carcinoma, followed by renal cell carcinoma. The longest DFI was in colorectal carcinoma. Due to the small sample of some types of primary tumours, for the purpose of the Kaplan-Meier analysis, we have combined those with less frequency as the “other” group (Fig. 1B). Patients with lung

carcinoma had shorter median survival (37.8 vs 96.7 months; log-rank test, $p = 0.028$) (Table 2) than patient with renal cell carcinoma. We observed a statistical dependence in terms DFI<12 months and DFI>12 months (log rank test; $p = 0.005$) (Fig. 1C, Table 2). The median survival of patients with DFI<12 months was 31.6 months, and for DFI>12 months - 59.1months. Of the patients with DFI < 12 months only 20% survived, while at DFI > 12 months 50% were still alive by the end of the follow-up (Table 1). Also, there was a difference in survival between the patients with REA and those with open adrenalectomy (log-rank test; $p = 0.016$), as the median survival of the first was 59.2 months, and of the second – 28.9 months (Fig. 1D, Table 2).

Fig. 1. Survival curves in a relationship with presentation (A), primary tumour (B), DFI (C) and surgical technique (D).

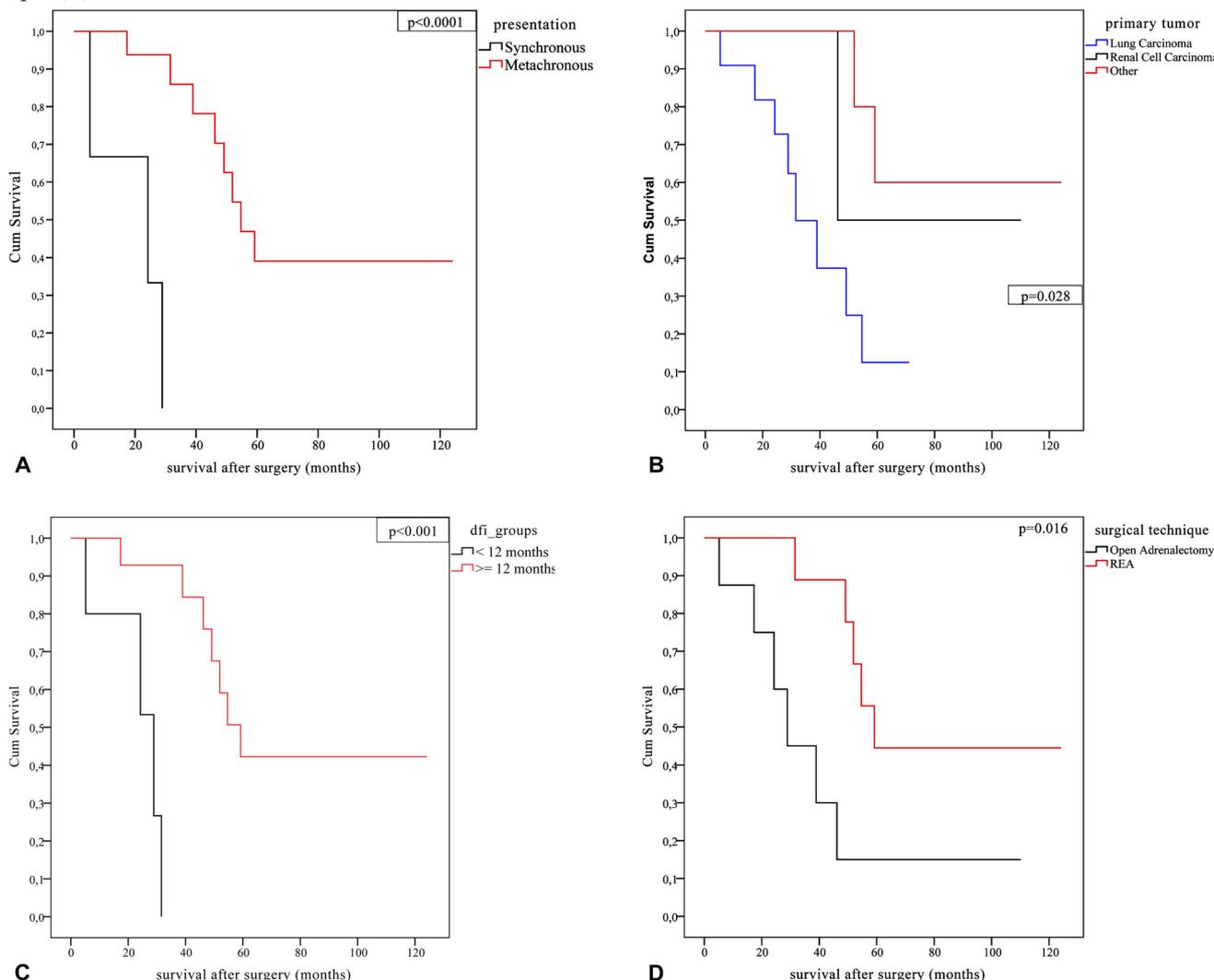


Table 3. Disease-free interval according to the primary tumour type in patients with isolated metastases

primary tumour	estimate
colorectal carcinoma ^a	127.4
lung carcinoma ^b	13.0
renal cell carcinoma ^b	30.3
breast carcinoma ^a	56.3
Other ^a	90.8

^a mean ^b median

DISCUSSION

The presence of metastases in the adrenal glands is usually associated with a poor prognosis, as it demonstrates a disseminated metastatic process. However, in cases of isolated adrenal metastases survival can be improved after adrenalectomy [3, 11-13]. In our 19 patients with isolated adrenal metastases, the mean estimate survival was 25.0 months, which according to the results of other authors [6, 15-17]. Xin Ma et al. [18] have reported median estimate

survival of 24 months, and 5-year survival of 6.1% in a group of 75 patients with adrenal metastases. Carlos Zerrweck et al. [19] are established median survival of 48 months and 5-year survival of 45% in a group of 65 patients, which is much more than the above-mentioned reports. In their analysis, the longest median survival (84 months) was found in carcinoma of the kidney, followed by colorectal carcinoma (29 months), and the shortest survival was for lung carcinoma (12 months). The authors demonstrated a longer median survival in patients with metastases under 5 cm size (21 patients) compared with metastases over 5 cm (73 vs. 20 months, $p=0.011$). Strong et al. [15] also have reported better survival for metastases under 4.5 cm, with a median survival in this group was 26 months, compared to 16 months in the group with metastases over 4.5 cm. In our patients we found no statistical difference between tumour size and overall survival (log-rank test; $p=0.621$), i.e. it was not to be a prognostic factor, as other authors have established in their studies and analyses [6, 14, 16, 17].

We have found that the type of tumour could serve as a prognostic factor for overall survival, with lung carcinoma demonstrating shorter survival compared to renal and

other types of cancer (log-rank test; $p=0.028$). The disease-free interval (DFI) was shorter for lung carcinoma, with median estimate survival of 13 months, followed by renal cell carcinoma – 30 months. The longest DFI was observed for colorectal carcinoma – 127 months. According to Lo et al. [3], patients with metastases from an adenocarcinoma had a better chance of survival. Muth et al. [17] have reported that patients with colorectal carcinoma have better outcomes than those with NSCLC. According to Paunovic et al. [8] the type of primary tumour does not influence survival. The survival difference between the different tumour types can be interpreted according to their biological behaviour.

According to certain authors [3, 17, 18], there was no significant survival between patients with synchronous and patients with metachronous metastases. According to other reports [6, 14, 15, 20], patients with metachronous metastases had better survival than those with synchronous. Similar to the latter, in our analysis, we estimated the same: patients with synchronous metastases have significantly shorter survival those patients with metachronous metastases, with median survival 24.2 vs. 54.7 (log-rank test; $p<0.0001$). No patients with synchronous metastases who survived the end of the follow-up period, while 50% of those with metachronous metastases were still alive. Therefore, synchronous metastases were associated with short survival, but not an independent prognostic factor in multivariate analysis. On the contrary, according to Eu Chang Hwang et al. [21], synchronous metastases were an independent prognostic factor for overall survival, reported as 59.4% ($n=19$) for synchronous cases with DFI of 8.8 months. Howell et al. [22] reported that patients with synchronous metastases had significantly shorter survival than metachronous, with a median survival of 14 vs. 41 months, and 5-year survival of 21% vs. 34%, respectively ($p=0.028$). He described in 19% ($n=11$) synchronous metastases with

DFI > 12 months in 39 (81%) and median overall survival – 30 months. Muth et al. [17] demonstrated that the metachronous group with DFI > 12 months was associated with 21-months longer median survival (log rank test, $p=0.03$). In a multivariate analysis, Paunovic et al. [8] demonstrated that DFI > 12 months was a statistically significant factor for better survival in patients with adrenalectomy due to metastases. In correspondence with the analyses of the above-mentioned authors, we also estimated that DFI > 12 months is a prognostic factor for better survival (log-rank test; $p=0.005$) – 27 months longer median survival, compared to the group with DFI < 12 months.

The first laparoscopic adrenalectomy (LA) for metastasis was carried out before 1999 by Heniford [11]. According to some authors [11, 12, 14, 16], it is a safe intervention and the oncological outcome is similar to that of open adrenalectomy (OA). Strong et al. [15] compared 31 LAs with 63 OAs. They described comparable rates of positive resection lines (22% vs 29%), local recurrence (11% vs 21%) and overall survival (median 31 months vs 30 months). Muth et al. [17] did not find any statistical correlation between survival and surgical technique. Our analysis showed a significant difference in survival between the retroperitoneal approach and conversion to open adrenalectomy (median survival 59.2 vs 28.9 months).

CONCLUSION

The minimally invasive approach has proven benefits in patients with isolated adrenal metastases, making it a reasonable first-choice in those cases. On the other hand, our analysis in correspondence with other similar studies allowed us to conclude that lung carcinoma, short DFI < 12 months, presence of synchronous tumours and male gender determine shorter survival after adrenalectomy due to metastasis, and this warrants us to predict the future outcome of the intervention.

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