Prognostic factors for survival after surgery for adrenal metastasis

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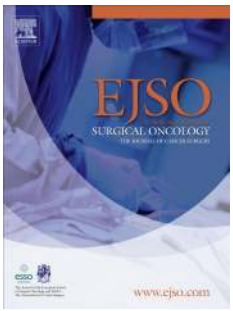

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ORIGINAL ARTICLE

Title: Prognostic factors for survival after surgery for adrenal metastasis

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ABSTRACT

Aim To better define the indications for adrenalectomy (adx) for adrenal metastasis we have analysed factors predicting survival in our institutional series.

Methods A consecutive series of 30 patients undergoing adx for metastasis (1996-2007), excluding patients with simultaneous ipsilateral renal cell carcinoma (RCC), was studied. Metastases were regarded as synchronous (<6 mo), or metachronous (>6 mo), depending on the interval after primary surgery. Survival was calculated from time of adx and risk factors influencing survival were identified.

Results The tumour diagnoses were RCC n=9, malignant melanoma n=5, non small-cell lung cancer n=5, colorectal carcinoma n=4, foregut carcinoid n=2, adrenocortical carcinoma, breast cancer, hepatocellular carcinoma, urothelial carcinoma, and liposarcoma (one each); nine adrenal metastases were synchronous and 21 metachronous. Ten patients had undergone previous surgery for extra-adrenal metastases. Out of 30 adx 10 were laparoscopic (LAdx) and 20 open (OAdx) procedures without surgical complications. The local recurrence rate was low: LAdx 1/10, OAdx 1/20, and the median survival was 23 months. Independent prognosticators of favourable survival were adx for potential cure (p=0.01), no previous metastasis surgery (p=0.02), and tumour type (p=0.043), with better prognosis for patients with adrenal metastasis from colorectal carcinoma and RCC and worse prognosis in non small-cell lung cancer and malignant melanoma.

Conclusions Surgery for adrenal metastasis is safe and the indication for this procedure in an individual patient can be supported by several prognostic factors. The survival benefit in patients with adx for potential cure indicates a therapeutic value of adx in selected patients.

Keywords Adrenal gland neoplasm/secondary; Adrenal gland neoplasm/surgery; Adrenalectomy; Follow-up studies

INTRODUCTION

Metastases to the adrenal glands are present in 13-27 percent of disseminated malignancies at autopsy [1, 2] with the highest figures for patients with pulmonary or renal primary tumours. However, isolated adrenal metastasis only occurs in less than one percent of these cases [3]. Adrenalectomy (adx) can render the patient tumour-free in case of isolated lesions, but the procedure can also be part of a staged treatment programme when multiple metastatic sites have been identified. Laparoscopic adx has been claimed to be a safe alternative in suspected or confirmed malignancy [4, 5]. Only few series reporting on indications and results of surgery for adrenal metastases have so far been published [6-12]. We have analysed our institutional series to identify prognostic factors for survival and further define the indications for surgical treatment.

PATIENTS AND METHODS

Patients A consecutive series of patients undergoing adx for metastasis to the adrenal gland (1996-2007) was studied, i.e. from the introduction of laparoscopic adx at our centre. Patients with direct extension of a primary tumour into the adrenal gland, or renal cell carcinoma (RCC) with ipsilateral synchronous adrenal metastasis, were not studied. The clinical information was gathered through patient records from our unit and referring hospitals. All histopathological reports were reviewed. Information on causes of death was retrieved from the Swedish Cause of Death Register. The study was approved by the Regional Ethical Review Board in Gothenburg.

Definitions Metastases were regarded as *synchronous* if detected within 6 months after primary surgery. Metastases discovered more than 6 months after primary surgery were defined as *metachronous*. *Disease-free interval (DFI)* was defined as the period of time the patient was tumour-free prior to detection of the adrenal metastasis. As a consequence, patients with an adrenal metastasis detected more than 6 months after primary surgery, but treated for another tumour manifestation within 6 months, thus have a metachronous adrenal metastasis with DFI less than 6 months. *Disease-free* and *overall survival* were calculated from time of adx up to tumour recurrence or death. *Adx for potential cure* was defined as a local R0 resection with no evidence of residual tumour at other sites.

Statistical analysis Overall and disease-free survival was calculated according to the Kaplan-Meier method. Patient gender, age at surgery, clinical presentation

(synchronous or metachronous tumour, DFI, previous metastasectomy), type of operation (open or laparoscopic), completeness of resection, size and histopathological diagnosis of the metastasis were evaluated using overall survival as the main outcome measure. Univariate comparisons of survival in different groups were performed with the log-rank test. Multiple stepwise Cox-regression [13] was used to construct a model relating survival to risk factors. The results given are from the final model. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics Thirty patients with adrenal metastasis (12 female, 18 male, mean (median) age 60.6 (62.5) years, range 30-79 years) were treated and fulfilled the inclusion criteria at our centre during the study period (Tab. 1). The diagnoses were RCC n=9, malignant melanoma n=5, non-small cell lung cancer (NSCLC) n=5, colorectal carcinoma n=4, foregut carcinoid n=2, adrenocortical carcinoma (metastasis to contralateral adrenal), breast cancer, hepatocellular carcinoma, urothelial carcinoma, and liposarcoma (one each).

Clinical presentation Nine patients had synchronous and 21 had metachronous adrenal metastasis; 10/21 had been subject to previous surgery for metastases. The mean (median) interval between primary surgery and detection of metastasis in the metachronous group was 80 (48) months, range 10-460, and mean (median) DFI was 10 (26) months, range 0-117. Nine patients had a DFI > 12 months.

Staging and diagnosis Preoperative work-up included computerized tomography (CT) of the abdomen (n=28), in 10 patients supplemented with abdominal magnetic resonance imaging (MRI). Three patients were staged with ^{18}F-fluorodeoxyglucose-PET-CT. Fine-needle aspiration cytology of the adrenal mass was performed in seven patients, confirming the diagnosis in five.

Surgical treatment The choice of surgical technique was up to the individual surgeon. Laparoscopic adx (LAdx) was preferred in isolated adrenal metastasis, while open adx (OAdx) was considered in multifocal disease or severe peritoneal

adhesions. 20 open adx (OAdx) and 10 LAdx were performed, the latter ones using the lateral transperitoneal approach. Three LAdx were converted to OAdx due to technical difficulties. OAdx was in eight patients combined with other surgical procedures: nephrectomy/renal resection in three, liver resection in two, splenectomy, cholecystectomy or bilateral adx in one patient each. The mean hospital stay after LAdx was four days, after OAdx ten days (p=0.05). The local recurrence rate was low in both groups (OAdx: 1/20, LAdx: 1/10, converted to OAdx) during a mean observation period of 35 and 16 months, respectively. No port-site metastases were observed. Adx for potential cure was achieved in 8/10 patients treated with LAdx and in 11/20 treated with OAdx.

There was no mortality associated with the surgical procedure. Two patients had non-fatal procedure-related complications (stroke and atrial fibrillation/heart failure, respectively). The first patient died four months postoperatively of a myocardial infarction, the other of progressive tumour disease 36 months after adx.

Follow-up, recurrence and survival Complete follow-up was available in all patients. Overall median survival (95% CI) was 23 (15-31) months with a 5-year actuarial survival rate of 22.5%. Median disease-free survival (95% CI) was 6 (0.9-11) months (Fig. 1A). Three patients are alive with no evidence of disease at 101, 60 and two months of follow-up. Five patients are alive with disease after 120, 52, 34, 24 and 16 months of follow-up. Twenty patients died of their tumour disease, two of other causes (traffic accident and myocardial infarction, respectively).

Adx for potential cure was associated with prolonged survival both in univariate and multivariate analyses, with a hazard ratio of 4.9 for patients with residual metastases (p=0.01) (Tab. 2, Fig. 1B). Previous metastasis surgery was a significant independent risk factor for worse prognosis with a hazard ratio of 5.8 in multivariate analysis (p=0.02) (Tab. 2, Fig. 1C). The mean interval (95% CI) between primary surgery and adx was 47 (2-93) months in patients without vs. 77 (31-123) months in patients with previous surgery for metastases (p=0.41). Significant differences in survival with regard to tumour type were seen (p=0.043), with longer survival for patients with colorectal carcinoma or renal cell carcinoma and shorter for those with non small-cell lung cancer (NSCLC) or malignant melanoma (Tab. 2, Fig 1D). The hazard ratio for death after metastasis surgery in patients with NSCLC vs. colorectal carcinoma was 37.6 (p=0.008). There was no statistically significant difference in survival between patients with synchronous or metachronous metastasis. However, in the metachronous group DFI > 12 months was associated with a 21 months longer median survival (log-rank test, p=0.03). No correlation between survival and gender, age at surgery, surgical technique (LAdx vs. OAdx) or size of the metastasis (> 45 mm vs. < 45 mm) was demonstrated.

DISCUSSION

Main findings In our consecutive 12-year series of 30 patients undergoing surgery for adrenal metastasis the overall median survival was 23 months with a 5-year actuarial survival rate of 22.5 %. This is in agreement with other investigators, e.g. Lo et al. [6] reported a 2-year survival rate of 40% in a series of 52 patients. Strong et al. [12], updating a previously published series [9], reported an actuarial survival rate of 37% (29/78) at 2 years, and of 17% (6/37) at 8 years; the series consisted of 92 patients. Castillo et al. [14] reported a mean survival of 26 months in a series of 22 cases. Sebag et al [11], found a median survival of 23 months in 16 patients; one-third was alive and disease-free at 5 years.

In our study adx for potential cure, previous metastasis surgery and tumour type were all independent prognostic factors for survival (Tab. 2). The significance of adx for potential cure as a prognostic factor has previously been identified by some [6, 7], but not other, authors [9, 12].

Impact of surgery on survival Whether adx alters the course of disease is not easily assessed in a setting of multiple metastatic sites subject to multimodal treatment. Randomized studies have not been performed. In a small case-control study Luketich & Burt [15] demonstrated a prolonged median survival in patients with NSCLC and synchronous solitary adrenal metastasis undergoing chemotherapy and adx vs. chemotherapy alone (31 vs. 8.5 months). In a review of patients with melanoma metastases, Mittendorf et al. [16] found longer survival in surgically treated cases compared to the entire patient group. The bias in the selection of adx

candidates is obvious. However, our finding that adx for potential cure was an independent factor for good prognosis supports a positive survival effect of adx.

Patient selection To select patients suited for adx leading to potential cure careful preoperative work-up, and optimal imaging, is necessary. With the refinement of CT diagnostics for adrenal lesions [17], dedicated adrenal CT is our method of choice for characterisation of the tumour. In line with this we no longer routinely use fine-needle aspiration cytology. ^{18}F-FDG-PET-CT was only performed in three patients in this series, but is now our standard procedure for staging [18, 19].

Surgical methods No difference in survival was seen with regard to the surgical technique in this series, in line with previous studies [9, 12]. The difference in potential curative adx rate between the LAdx and OAdx probably reflects our preference for open surgery in patients with multi-focal disease. The rate of local recurrence was low in both adx groups. However, LAdx was associated with a much shorter hospital stay than OAdx and for patients with isolated metastasis we now prefer LAdx.

Prognostic factors for survival Tumour type was early suggested to be a prognostic factor leading to better survival in patients with metastases from adenocarcinoma [6]. In our series tumour type was a significant prognosticator with the most favourable outcome for patients with colorectal carcinoma; the shortest survival was seen in patients with NSCLC (Fig. 1D).

Previous surgery for metastases was an independent negative prognostic factor in our series, i.e. the adrenal metastasis might represent a late manifestation of tumour disease (Fig 1C). However, the time interval between primary surgery and detection of the adrenal metastasis was not significantly longer in these patients than in those without previous metastasis surgery. Ten out of 30 patients in our series had undergone previous surgery for metastases compared to 22% in the report by Sarela et al. [9] and 56% reported by Sebag et al. [11].

DFI can be regarded as a surrogate marker for tumour aggressiveness. It seems reasonable to assume that patients with a long disease-free period have a more indolent course and therefore a better prognosis. In a study on adrenal metastases of NSCLC by Mercier et al. [10], and in the first two reports from the Memorial Sloan-Kettering Cancer Center [7, 9], metachronous tumours were associated with better prognosis. In the updated MSKCC series this association was no longer evident [12] and has not been confirmed by other authors [6, 8, 11]. In the literature, DFI has been defined as the time interval between primary surgery and detection of the adrenal metastasis, not taking surgery for other tumour manifestations into account. We used a strict definition of DFI *as the period of time the patient was objectively tumour-free prior to the recognition of adrenal metastasis*. With this definition DFI > 12 months was a positive prognostic factor in patients with metachronous metastasis.

In contrast to the present and other reports [7, 9, 11] Strong et al. [12] found that adrenal metastases with large diameter (>45 mm) were associated with worse prognosis. Almost half (42%) of their patients had lung cancer and tumour size may

more accurately correlate to tumour aggressiveness in less heterogenous patient series.

Analyses of prognostic factors in case-series are hampered by selection bias and many variables are closely inter-related. The small number of patients in the non-randomised studies published further adds to the complexity. A larger pooled analysis using strict definitions and standardised protocols would help to identify the optimal indications for adx for adrenal metastasis. In larger patient materials more precise identification of tumour characteristics, including molecular markers, could lead us to tailored treatment of individual patients.

Conclusions Adx should always be considered for isolated adrenal metastasis but also in patients undergoing multi-modal treatment for metastatic disease. The median survival in this series was 23 months with low perioperative morbidity. Factors associated with longer survival were tumour type (best for colorectal carcinoma), no prior surgery for metastases, long disease-free interval and potentially curative adx at time of surgery.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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FIGURE CAPTIONS

Table 1: Clinical characteristics of patients operated for adrenal metastasis. Abbreviations: Age = age at surgery. OAdx/LAdx = open/laparoscopic adrenalectomy. Conv. = converted to open surgery. RCC = clear cell renal carcinoma. NSCLC = non small-cell lung cancer. DFS = disease-free survival (months). FU = follow-up (months). Status at follow-up: AWD = alive with disease. DOC = dead of other cause. DOD = dead of disease. NED = no evidence of disease. Please note that patients with metachronous metastasis and other tumour manifestations after primary surgery may have a disease-free interval (DFI) < 6 months.

Table 2: Univariate and multivariate analysis of overall survival with respect to eight different background variables.

Figure 1: Survival analysis according to Kaplan and Meier showing overall and disease-free survival (A), if the procedure was potentially curative or not (B), if previous metastasectomy had been performed or not (C), and survival in relation to tumour type (D). Patients at risk are tabulated below the figures. P-values are from the multivariate analysis. Abbreviations: OS = overall survival, DFS = disease-free survival, CRC = colorectal carcinoma, MM = malignant melanoma, NSCLC = non small-cell lung cancer, RCC = renal cell carcinoma, Adx +/- = Adrenalectomy for potential cure achieved/not achieved, PM +/- = previous metastasectomy performed/not performed.

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Table 1

No	Sex	Age	Presentation	DFI (mo.)	Previous metastasectomy	Technique	Histopathology	Adx for potential cure	DFS (mo.)	FU (mo.)	Status
1	M	33	Metachronous	10	Yes	OAdx	Malignant melanoma	No	0	11	DOD
2	M	42	Metachronous	2	Yes	LAdx (conv.)	Urotelial carcinoma	No	0	15	DOD
3	M	51	Synchronous	0	No	OAdx	RCC	Yes	93	120	AWD
4	M	30	Metachronous	10	Yes	LAdx	Myxoid liposarcoma	Yes	3	38	DOD
5	M	68	Metachronous	5	Yes	LAdx	Colorectal carcinoma	Yes	12	23	DOD
6	M	45	Synchronous	0	No	LAdx	Hepatocellular carcinoma	Yes	19	20	DOD
7	F	58	Synchronous	6	No	OAdx	RCC	Yes	13	26	DOD
8	M	62	Metachronous	52	No	OAdx	Foregut carcinoid	No	0	25	DOD
9	F	63	Synchronous	0	No	OAdx	NSCLC	No	0	15	DOD
10	M	64	Metachronous	117	No	OAdx	RCC	Yes	101	101	NED
11	M	57	Synchronous	0	No	OAdx	RCC	Yes	36	76	DOD
12	F	65	Metachronous	21	No	LAdx (conv.)	NSCLC	Yes	13	24	DOD
13	M	78	Synchronous	0	No	LAdx	NSCLC	No	0	6	DOC
14	M	75	Synchronous	0	No	OAdx	RCC	No	0	4	DOD
15	F	65	Metachronous	28	No	OAdx	RCC	Yes	12	51	DOD
16	M	62	Synchronous	0	No	OAdx	Foregut carcinoid	No	0	12	DOD
17	F	60	Metachronous	68	No	OAdx	Breast cancer	Yes	60	60	NED
18	F	59	Metachronous	10	No	LAdx	NSCLC	Yes	7	12	DOD
19	F	73	Metachronous	47	No	OAdx	RCC	Yes	14	36	DOD
20	M	57	Metachronous	37	Yes	OAdx	Colorectal carcinoma	Yes	22	52	AWD
21	F	78	Metachronous	38	Yes	OAdx	Malignant melanoma	Yes	6	19	DOD
22	M	58	Metachronous	0	No	OAdx	RCC	No	0	14	DOC
23	M	65	Metachronous	0	Yes	OAdx	Malignant melanoma	No	0	34	AWD
24	F	68	Synchronous	0	No	OAdx	NSCLC	No	0	2	DOD
25	M	67	Metachronous	0	No	OAdx	Malignant melanoma	No	0	16	DOD
26	F	57	Metachronous	5	Yes	LAdx	Colorectal carcinoma	Yes	7	24	AWD
27	M	79	Metachronous	3	Yes	LAdx	Malignant melanoma	Yes	3	4	DOD
28	F	71	Metachronous	7	No	OAdx	Colorectal carcinoma	Yes	8	16	AWD
29	F	44	Metachronous	0	Yes	OAdx	Adrenocortical carcinoma	Yes	1	11	DOD
30	M	64	Metachronous	85	No	LAdx (conv.)	RCC	Yes	2.0	2	NED

Table 2:

Variable	Mean survival in months (95% CI)	Univariate Analysis (p-value)	Multivariate analysis (p-value)	Hazard ratio
Gender		0.86	n.s.	
male (n=18)	28 (18-39)			
female (n=12)	28 (17-39)			
Tumour type		0.023	0.043	
colorectal cancer (n=4)	42 (27-58)			1.0[a]
renal cell carcinoma (n=9)	56 (26-85)		0.10[a]	8.5[a]
malignant melanoma (n=5)	17 (8-26)		0.13[a]	6.2[a]
non-small cell lung cancer (n=5)	12 (4-19)		0.008[a]	37.6[a]
other (n=7)	26 (14-38)		0.16[a]	4.7[a]
Presentation		0.37	n.s.	
synchronous (n=9)	31 (6-56)			
metachronous (n=21)	40 (23-54)			
Disease-free interval		0.028	n.s.	
metachronous DFI<12 months (n=12)	21 (14-29)			
metachronous DFI>12 months (n=9)	57 (33-82)			
Previous metastasectomy		0.53	0.02	5.8
no (n=20)	42 (23-60)			
yes (n=10)	24 (14-35)			
Size of metastasis		1.00	n.s.	
< 45 mm (n=12)	40 (16-64)			
> 45 mm (n=18)	36 (19-52)			
Surgical technique (OA/LA)		0.14	n.s.	
LA (n=10)	20 (12-28)			
OA (n=20)	46 (26-66)			
Adrenalectomy for potential cure		0.02	0.01	4.9[b]
achieved (n=19)	51 (31-72)			
not achieved (n=11)	14 (9-19)			

[a] Versus colorectal carcinoma. [b] Adx for potential cure.not achieved vs. achieved

Figure 1: