Master's degree

Factors related to improved clinical outcomes associated with adrenalectomy for metachronous adrenal metastases from solid primary carcinomas

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Abstract

Background: Surgery for metachronous adrenal metastases from solid primary carcinoma has increased with the development of technical skills. Here we analyzed the postoperative clinical outcomes of patients who underwent adrenalectomy for metachronous adrenal metastases from solid primary carcinomas.

Methods: Patients who underwent adrenalectomy for metachronous adrenal metastases after initial treatment of primary carcinoma at Asan Medical Center from 2000 to 2010 were included. Clinicopathological parameters were analyzed to evaluate prognostic outcomes.

Results: A total of 30 patients with 19 hepatocellular carcinomas and 11 lung carcinomas were included. The mean age was 54.3 years. The mean time until adrenalectomy was 23 months. The size of the metastatic adrenal tumor and the disease status of the primary carcinoma at the time of adrenalectomy were associated with second recurrence after adrenalectomy ($P < 0.05$). There was no significant difference in disease-specific recurrence-free survival between patients who underwent open adrenalectomy and laparoscopic adrenalectomy ($P = 0.646$).

Conclusions: Surgical treatment should be recommended for metachronous adrenal metastases in patients with no evidence of primary carcinoma and/or in those having metastatic adrenal tumors ≤4.4 cm. This approach may increase the recurrence-free interval related to second recurrence. Further, laparoscopic adrenalectomy appears sufficient for the treatment of such patients.

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Introduction

Adrenal metastases from solid primary carcinoma is relatively common with a prevalence of 10%–25% in all carcinoma patients.[1)] With the development of imaging modalities, the incidental detection of adrenal gland lesions, either at the time of initial diagnosis or during follow-up, has increased.[2,3)] Adrenal metastases commonly occurs in patients with lung or gastrointestinal carcinomas.[4)]

Distant metastasis from a carcinoma can be divided into synchronous and metachronous metastasis. Synchronous metastasis is typically associated with a poor prognosis because of the advanced stage at the time of diagnosis and requires multiple further treatments. However, metachronous adrenal metastasis has been shown to have favorable outcomes in certain studies, with some supporting the resection of metastatic adrenal tumors with curative intent in selected patients when there is no evidence of other metastatic lesions.[5-7)]

In addition, the type of surgical approach used to manage adrenal metastasis may affect surgical outcomes. In the early days, open adrenalectomy (OA) was the only choice of surgical method. However, laparoscopic adrenalectomy (LA) has been performed in cases of malignant adrenal lesions with tolerable surgical outcomes since its development.[4,8-10)]

The aims of the present study were to analyze clinical outcomes after adrenalectomy for metachronous adrenal metastases, identify factors related to improved clinical outcomes, and support patients expected to benefit from adrenalectomy. In addition, we compared patient outcomes between OA and LA.

Material and Methods

Study population

Patients with metachronous adrenal metastases from solid primary carcinomas treated with adrenalectomy in Asan Medical Center, Seoul, Korea from January 2000 to December 2010 were selected. The study protocol was approved by our institutional review board, and the requirement for informed consent from each patient was waived.

We included patients who presented metachronous adrenal metastases on imaging studies after initial treatment of primary carcinoma that was pathologically proven after adrenalectomy. During this period, 77 patients underwent adrenalectomy for metastases.

After a review of medical records, patients with synchronous metastasis, multiple metastases, or missing medical records were excluded. Eight cases having either only 1 or 3 patients for each cancer type were excluded in this study because these patients' data was not sufficient enough to draw any meaningful results; 3 colorectal cancer, 2 sarcoma, 1 bladder cancer, 1 breast cancer and 1 renal cancer. Finally, 30 patients were included in the present study. At the last follow up, five patients are still alive. For further analysis, we divided all patients into two groups according to the presence of second recurrence after adrenalectomy: no second recurrence group and second recurrence group.

Follow-up protocols

All patients underwent postoperative imaging, including abdominopelvic computed tomography (CT), chest CT, magnetic resonance imaging (MRI), and/or positron emission tomography (PET) for evaluation. Adrenal metastasis was diagnosed by CT, MRI, and/or PET during the follow-up period and confirmed by histopathological reports after adrenalectomy. Routine follow-up examinations were conducted every 6–12 months according to the patient's clinical condition.

Prognostic outcomes

For each patient, clinical data, including age, sex, origin of primary carcinoma, date of initial treatment, date of adrenalectomy, site of adrenal metastasis, metastatic adrenal tumor size, type of adrenalectomy, disease-specific interval (DSI), disease-specific recurrence-free survival (RFS), and overall survival (OS), were analyzed. DSI was defined as the time interval between the date of initial primary carcinoma treatment and the date of adrenalectomy. Disease-specific RFS was defined as the time interval between the date of adrenalectomy and the date of second recurrence (locoregional area and/or distant metastasis) after adrenalectomy. OS was defined as the time interval between initial primary carcinoma treatment and the last follow-up date. Factors related to second recurrence after adrenalectomy were analyzed.

Statistics

Continuous variables are presented as mean ± standard deviation with ranges, and categorical variables are presented as percentages and absolute numbers. Univariate and multivariate Cox proportional hazards modeling analyses were performed to identify risk factors for second recurrence. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. For clinical applicability, the area under the curve (AUC) was calculated using receiver operating characteristic (ROC) curve analysis in order to evaluate the cutoff value for continuous variables with significance. Scatter plots with Pearson's correlation were used to show the main trend between DSI and disease-specific RFS. Survival outcomes were analyzed using the Kaplan–Meier method and log-rank tests. P values of <0.05 were considered statistically significant. Analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, USA).

Results

A total of 30 patients with metachronous adrenal metastasis from solid primary carcinoma were included. The mean age was 54.3 years. The male:female ratio was 26:4. Hepatocellular carcinoma was the major primary carcinoma (n = 19; 63.3%), followed by lung carcinoma (LC; n = 11; 36.7%). Eighteen patients underwent surgical resection of the primary carcinoma with curative intent, whereas 12 patients received treatments other than surgery (chemoradiation, 3; transarterial chemoembolization, 9). The mean metastatic adrenal tumor size was 5.0 cm. In total, 19 (63.3%) patients underwent OA and 11 (36.7%) underwent LA. In terms of disease status at the time of adrenalectomy, 18 (60%) patients had no evidence of disease (NED) and 12 (40%) had persistent disease related to the primary carcinoma. The mean DSI was 23.2 months. Second recurrence (either in the locoregional area or distant metastasis) after adrenalectomy occurred in 26 (86.7%) patients, with a disease-specific RFS of 23.4 months (Table 1).

Factors related to second recurrence after adrenalectomy were analyzed (Table 2). There was a significant difference in patient age between the no second recurrence and second recurrence groups, with younger age found to be associated with second recurrence (P = 0.036). There was no statistical difference in metastatic adrenal tumor size, site of adrenal metastasis, type of adrenalectomy, and disease status at the time of adrenalectomy between

the two groups (P > 0.05).

Table 1.

Characteristics	n = 30	% (range)
Age (years)	54.3 ± 11.14	(36–75)
Sex		
Male	26	86.7%
Female	4	13.3%
Types of primary carcinoma		
Hepatocellular carcinoma	19	63.3%
Pulmonary carcinoma	11	36.7%
Primary carcinoma treatment		
Surgery	18	60.0%
Other treatment	12	40.0%
Size of metastatic adrenal tumor (cm)	5.0 ± 2.23	(1.5–9.2)
Site of adrenal metastasis		
Left	18	60.0%
Right	12	40.0%
Type of adrenalectomy		
Open adrenalectomy	19	63.3%
Laparoscopic adrenalectomy	11	36.7%
Status at the time of adrenalectomy		
No evidence of disease	18	60.0%
Persistent disease	12	40.0%
Disease-specific interval (months)	23.2 ± 20.28	(5–99)
Second recurrence after adrenalectomy	26	86.7%
Disease-specific recurrence-free survival (months)	23.4 ± 28.53	(1–132)
Overall survival (months)	65.5 ± 47.49	(13–182)

:Clinical characteristics of patients who underwent adrenalectomy for metachronous adrenal metastases from other primary carcinomas after initial treatment

There was no significant difference in DSI (P = 0.055); however, the mean interval between initial treatment of primary carcinoma and adrenalectomy appeared to be longer in the no second recurrence group compared to the second recurrence group (DSI, 41.3 vs 20.5 months, respectively). In univariate analysis, the metastatic adrenal tumor size (P = 0.018) was found to be associated with second recurrence (HR, 1.270; 95% CI, 1.04–1.55). The ROC curve was calculated and the cutoff value of the metastatic adrenal tumor size related to second recurrence was >4.4 cm (AUC, 0.668).

Although disease status at the time of adrenalectomy was not found to be associated with

Table 2.

Characteristics	No second Recurrence		Second Recurrence		p value	Univariate		Multivariate	
	(n = 4)	% (range)	(n= 26)	% (range)		HRs (95% CI)	p value	HRs (95% CI)	p value
Age (years)	65.0 ± 6.88	(60–75)	52.6 ± 10.82	(36–72)	0.036	0.97 (0.93–1.01)	0.146	0.98 (0.94–1.03)	0.449
Sex		0.0%			0.461				
Male	3	75.0%	23	88.5%					
Female	1	25.0%	3	11.5%		1.54 (0.46–5.18)	0.482	0.84 (0.19–3.76)	0.823
Primary carcinoma treatment					0.661				
Surgery	2	50.0%	16	61.5%					
Other treatment	2	50.0%	10	38.5%		1.51 (0.67–3.43)	0.320	2.01 (0.80–5.07)	0.137
Size of metastatic adrenal tumor (cm)	3.7 ± 1.95	(1.5–6.0)	5.2 ± 2.24	(2.0–9.2)	0.226	1.27 (1.04–1.55)	0.018	1.27 (0.98–1.64)	0.072
Site of adrenal metastasis					0.511				
Left	3	75.0%	15	57.7%					
Right	1	25.0%	11	42.3%		1.12 (0.51–2.46)	0.772	1.1 (0.48–2.74)	0.805
Type of adrenalectomy					0.603				
Open adrenalectomy	1	25.0%	10	38.5%					
Laparoscopic adrenalectomy	3	75.0%	16	61.5%		1.21 (0.54–2.70)	0.646	1.03 (0.41–2.56)	0.956

Status at the time of adrenalectomy					0.511				
No evidence of disease	3	75.0%	15	57.7%		0.45(0.19–1.00)	0.051	0.42(0.18–1.02)	0.055
Persistent disease	1	25.0%	11	42.3%					
Disease-specific interval	41.3 ± 39.20	(13–99)	20.46 ± 15.26	(5–54)	0.055	0.98(0.96–1.01)	0.109	0.97(0.93–1.01)	0.187

HRs: Hazard ratio, CI: Confidence interval

Univariate and multivariate Cox regression analyses of risk factors related to second recurrence in patients who underwent adrenalectomy for metachronous adrenal metastases from other primary carcinomas after initial treatment

second recurrence (P = 0.051; Table 2), the disease-specific RFS related to the second recurrence was found to significantly differ between the NED group and persistent disease group with primary carcinoma at the time of adrenalectomy, and the NED group presented a greater interval between adrenalectomy and second recurrence (P = 0.038; Fig 1).

Because 87.7% of patients presented with second recurrence, the relationship between DSI and disease-specific RFS was analyzed to determine whether the interval until adrenalectomy affected the interval between adrenalectomy and second recurrence. In the scatter plot with Pearson's correlation, a positive relationship was observed between DSI and disease-specific RFS with a statistically significant difference (P = 0.045; Fig 2).

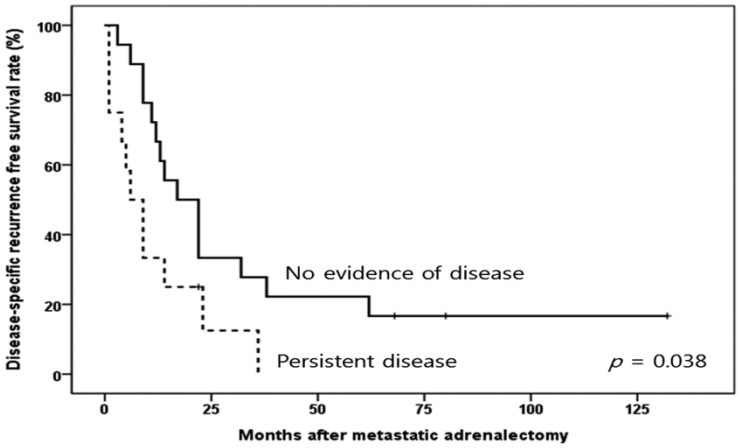

Fig 1. Disease-specific recurrence-free survival curves according to the disease status of primary carcinoma after adrenalectomy (P = 0.038).

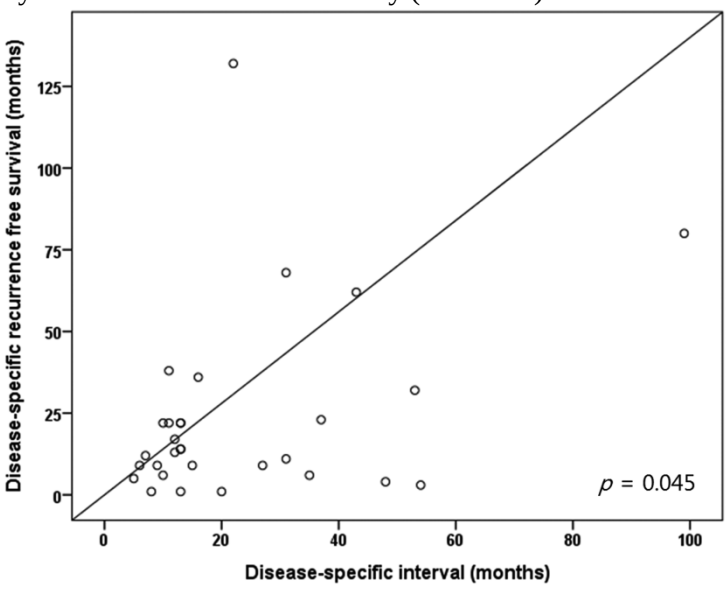

Fig 2. Scatter plot demonstrating the correlation between the disease-specific interval and disease-specific recurrence-free survival (P = 0.045).

Discussion

In the present study, the clinical outcomes of patients with metachronous adrenal metastasis from solid primary carcinomas were evaluated to identify factors associated with second recurrence and change in survival after adrenalectomy. A significant difference in patient age was observed between the subdivided recurrence-related groups. DSI for the interval between the date of initial primary carcinoma treatment and the date of adrenalectomy related to second recurrence did not significantly differ between the two groups; however, this difference had marginal significance. Metastatic adrenal tumor size was identified as a risk factor on univariate analysis. Although the disease status of the primary carcinoma at the time of adrenalectomy had no statistical significance, it was related to disease-specific RFS with NED patients having a longer interval to second recurrence. Finally, DSI and disease-specific RFS showed a positive correlation with second recurrence.

Patient age significantly differed between the no second recurrence and second recurrence groups, with patients in the second recurrence group having a younger mean age. This finding may be related to the potential risk of developing second recurrence in terms of longer possible life period in patients diagnosed with primary carcinoma at a younger age rather than those diagnosed at an older age necessarily having a decreased risk of recurrence in comparison.

Several studies have reported DSI as a prognostic or predictive factor of postoperative outcomes in adrenal metastases. Solaini *et al*.[11] reported a long DSI as a positive prognostic factor, Muth *et al*.[12] and Howell *et al*.[13] found that patients with a DSI of ≥12 months had a longer median survival than those with a DSI of <12 months (41 vs. 13 months). Sarela *et al*.[14] and Kim *et al*.[5] reported a DSI of >6 months as the only factor associated with improved survival. However, in the present study, DSI was not found to be statistically significantly different. This result may differ if additional cases are evaluated in future studies.

Earlier studies have evaluated the relationship between the metastatic adrenal tumor size and long-term survival. Marangos *et al*.[15] and Strong *et al*.[8] reported that there was no significant difference in survival when comparing small (<6 cm) and large (>6 cm) tumors among 41 patients with adrenal metastases in whom surgical resection was performed (P =

0.84). Tomasini *et al.*[16] also reported the feasibility of adrenalectomy in adrenal metastases regardless of the tumor size or primary carcinoma type. In the present study, there was a significant difference in metastatic adrenal tumor size on univariate analysis, with a <4.4 cm metastatic tumor size found to be associated with longer disease-specific RFS. Thus, based on the results of the present study and other previous studies, when the metastatic adrenal tumor size is <4.4 cm at the time of adrenalectomy, the time interval to second recurrence may be longer than that for larger-sized tumors.

The disease status of the primary carcinoma at the time of adrenalectomy demonstrated a significant difference in disease-specific RFS, with NED patients found to have a longer interval until second recurrence. Therefore, when metachronous adrenal metastasis is diagnosed in NED patients, adrenalectomy should be recommended to increase the interval to second recurrence. In addition, the longer DSI was positively related to longer disease-specific RFS.

Since Gagner *et al.*[17] first described LA in 1992, it has become the gold standard for the management of benign adrenal masses.[18] However, LA for solitary metastasis or primary adrenal carcinoma remains controversial because of the possibility of carcinomatosis, port-site metastasis, and lack of studies with affirmative oncological outcomes.[9,19] Recently, laparoscopic indications have been expanded and surgical removal of the adrenal gland for isolated metastatic disease has become more acceptable, with reports describing long-term survival after LA.[8,9,20,21] LA may be associated with decreased intraoperative blood loss, shorter length of hospital stay, and superior cosmetic compared with OA.[14,22] Several studies have assessed the feasibility of adrenalectomy for adrenal metastases.[4,5,8,10,14,15,19] However, the majority have focused on comparing outcomes between OA and LA. Only few studies have assessed patient survival after adrenalectomy in a small number of cases.[5,11,16,20,23,24] Moreno *et a.l.*[25] reported a multicenter study about metastatic adrenalectomy showing overall generalized clinicopathologic outcomes that surgical removal is associated with long-term survival in few patients. Moreover, there are few studies that have assessed prognostic or predictive factors related to improved survival following adrenalectomy. In the present study, we found no significant difference between OA and LA in terms of disease-specific RFS, which indicates that LA is non-inferior to OA in terms of surgical benefit (P = 0.603).

A limitation of the present study was that the number of patients treated using adrenalectomy was small and the prognostic process may have differed between patients as the general condition of each patient was not standardized. Furthermore, because this was a retrospective study, the indications for performing adrenalectomy could not be clearly determined; this may have biased survival outcomes.

Conclusion

Adrenalectomy is a treatment option for metachronous adrenal metastasis from solid primary carcinomas diagnosed when the primary carcinoma has NED status and has a size of <4.4 cm. This approach appears to improve clinical outcomes related to second recurrence. An increased interval between initial primary carcinoma treatment and adrenalectomy may lengthen the disease-specific RFS. Furthermore, LA was found to be non-inferior to OA in terms of patient outcomes.

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국문요약

영상장비 및 진단기법의 발전으로 전이성 부신암은 비교적 흔하게 접할 수 있게 되었다. 그 중에서 일차성 고형암에서 이시성으로 발생한 전이성 부신암은 이전 연구들에서 수술하였을 때, 동시성 전이 부신암과 비교하여 더 나은 결과를 보고하였다. 또한 복강경 절제술이 부신병변에 대해 표준 술식으로 되어감에 따라 이를 부신암에도 적용 가능한지에 대해 논란이 있었다. 이에 본원에서 2000년부터 2010년까지 일차성 고형암에서 이시성으로 발생한 부신암으로 수술한 30명의 환자들은 분석한 결과 부신절제술 당시 무병상태를 유지하였던 환자에서 질병-특이 무병 생존기간이 더 길었다. 2차 재발과 관련된 요소로는 일차암 치료 후 부신에 전이암이 발생하기까지의 기간이 길수록 질병-특이 무병 생존기간이 더 긴 양의 상관관계를 보였으며 부신암 크기가 4.4cm 이하일 경우에 더 낮은 2차 재발률을 보였다. 복강경은 개복수술과 비교하여 2차 재발에 유의한 차이를 보이지 않았다. 이를 통해 미루어 볼 때, 무병상태를 유지하고 있는 이시성으로 발생한 전이 부신암 환자에서, 크기가 4.4cm 이하일 때 부신절제술을 2차 재발까지의 기간을 늘리기 위한 치료의 한 방법으로 고려 해 볼 수 있다. 그리고 부신절제술을 시행할 때 가능하다면 복강경 접근으로 시도해 볼 수 있다.