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Prognostic factors for recurrence-free and overall survival after adrenalectomy for metastatic carcinoma: a retrospective cohort pilot study

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Abstract

Background: The survival benefits of adrenalectomy (ADx) in the setting of metastatic cancer and prognostic factors for recurrence-free (RFS) and overall survival (OS) after adrenalectomy for metastatic carcinoma are still under debate. We evaluated the impact of clinicopathological variables on RFS and OS after ADx for metastatic carcinoma in patients with primary cancer.

Methods: A total of 32 patients undergoing ADx for metastatic cancer between 2004 and 2012 at two tertiary medical centers. Metastases were regarded as synchronous (<6 months) or metachronous (≥6 months) depending on the interval after primary surgery. Associations of perioperative clinicopathologic variables with RFS and OS were analyzed using Cox regression models.

Results: In total, 32 patients received ADx for metastatic primary tumors located in the lung (n = 11), colon (n = 4), liver (n = 5), stomach (n = 3), kidney (n = 4), pancreas (n = 2), glottis, esophagus, cervix, and ovary (n = 1 each). The overall recurrence rate after adrenalectomy was 62.5% (n = 20). By univariate analysis, C-reactive protein, inflammation-based prognosis score, and adrenalectomy for curative intent were associated with RFS and OS. Independent prognostic factors for shorter RFS were operative method (laparoscopy HR 4.68, 95% CI 1.61-13.61, p = 0.005) and inflammation-based prognostic score (HR 11.8, 95% CI 2.50-55.7, p = 0.002). For shorter OS, synchronous metastasis (HR 3.05, 95% CI 1.07-11.94, p = 0.048) and inflammation-based prognostic score (HR 6.65, 95% CI 1.25-35.23, p = 0.026) were identified as independent prognostic factors.

Conclusions: Our pilot study suggests that synchronous disease and inflammation-based prognostic score are significant prognostic factors for survival and should be considered when performing ADx for metastatic diseases.

Keywords: Adrenalectomy, Neoplasm metastasis, Prognosis, Survival

Background

The adrenal glands are a common site of metastases from a variable primary cancer. Approximately 25% of patients with primary cancer are found at autopsy to have metastases to their adrenal glands [1]. Indeed, it has been estimated that, in patients with a history of a previous malignancy, over 50% of newly discovered adrenal lesions are metastatic [2].

Advances in oncological and surgical therapies have led to a significant increase in the life expectancy of cancer patients and have also prolonged survival of patients with isolated or multiple metastases. Although the overall prognosis for metastatic cancer in the adrenal glands is poor, the survival duration is longer in patients who undergo adrenalectomy for metastatic cancer in comparison to that in patients who undergo resection of metastases in other visceral sites, such as the liver and lung, because adrenal metastasis is often confined within the adrenal gland itself, providing more chances to achieve en bloc removal [3-6]. It seems reasonable to apply similar criteria for selecting patients for resection of adrenal

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metastases, including control of extra-adrenal disease, a reasonably long disease-free interval, an acceptable patient performance status, and the absence of significant comorbidity [2]. In this regard, several studies have reported survival benefits of adrenalectomy (ADx) in the setting of metastatic cancer [7,8] Nevertheless, the prognostic factors for recurrence-free (RFS) and overall survival (OS) after adrenalectomy for metastatic carcinoma are still under debate [8-11]. Therefore, we evaluated the impacts of clinicopathological variables on the RFS and OS after ADx for metastatic carcinoma in patients with primary cancer.

Methods

Patients
At two tertiary medical centers in Korea (Chonnam National University Hwasun Hospital and Korea University Anam Hospital), a total of 32 patients received ADx for metastasis to the adrenal gland, irrespective of the primary cancer type, between January 2004 and December 2012. Clinical indicated metastasis was evaluated using a combination of endoscopy, computed tomographic scans of the chest and abdomen, and positron emission tomography or bone scans. The criteria for inclusion in the present study of ADx for adrenal metastasis were as follows: (1) histologically confirmed primary cancer and adrenal metastasis; (2) presence of synchronous (primary diagnosis to adrenalectomy less than six months) or metachronous (primary diagnosis to adrenalectomy more than six months) adrenal metastasis. Patients with renal cell carcinoma (RCC) with synchronous adrenal metastasis (ipsilateral or contralateral) or direct invasion of a primary cancer in the adrenal gland were excluded. Intent to treat was divided into cure and palliation. Cure was defined as a curative margin-negative (R0) resection with no evidence of residual tumor at another site. Palliation was defined as a surgical resection for symptom relief or margin-positive (R1) resection with no evidence of residual tumor at another site. Data regarding patient demographics, RFS and OS were obtained by medical record review. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed throughout. The study protocol was reviewed by the Institutional Review Board of Chonnam National University Hwasun Hospital and Korea University Anam Hospital and they waived the need for ethical approval in both institutions.

Measurement of serum CRP and definition of Glasgow Prognostic Score (GPS)
Routine laboratory testing of serum CRP and albumin was performed before ADx. Serum CRP was measured by latex turbidimetric immunoassay using a HITACHI 7600 analyzer (Hitachi, Tokyo, Japan). The CRP limit of detection was 0.03 mg/dl, and 1.0 mg/dl was the upper limit of the normal range. Coefficients of variation over the range of measurements were < 5%.

Each GPS was assigned as follows: patients with both elevated CRP (>1.0 mg/dl) and low albumin (<3.5 mg/dl) received a score of 2, whereas those with only one or none of these biochemical abnormalities earned scores of 1 and 0, respectively.

Statistics
Univariate and multivariate analyses (stepwise forward procedure) were performed using Cox proportional hazard analysis to identify risk factors affecting overall survival (OS) and recurrence-free survival (RFS). OS was defined as the period from ADx to the date of death from any cause. RFS was defined as the period from ADx to the date of disease progression or death, whichever occurred first. If neither event had occurred at the time of the last record, the patient was censored at that time. The factors included in the model were age, sex, ECOG PS, operative method (open or laparoscopic), intent to treat (palliation or cure), interval of primary diagnosis to adrenalectomy (synchronous vs. metachronous), site of metastasis, site of primary tumor, previous metastasectomy, C-reactive protein, serum albumin, and GPS. Among the factors, those with p < 0.25 were selected (on univariate analysis for RFS and OS) and included in the multivariate regression analysis using Cox proportional hazards regression model, which was performed to achieve adjusted hazard ratio (HR) to determine prognostic factors for recurrence free and overall survival. A two-tailed p < 0.05 was considered significant for all analyses. The SPSS software package, version 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Patient demographics
The baseline characteristics of the 32 patients are shown in Table 1. The median patient age was 63.5 years (range, 35–82 years). The median follow-up time (from adrenalectomy to death or last follow-up date) was 10.4 months (range, 0.5-74.3 months), and median time to adrenalectomy after primary cancer diagnosis was 8.8 months (range, 0–93.8 months). A total of 27 patients (84.4%) were male, and five patients (15.6%) were female. Nineteen patients (59.4%) had synchronous adrenal metastasis and 13 had metachronous adrenal metastasis. The diagnoses of primary cancer were lung cancer (n = 11), liver cancer (n = 5), kidney cancer (n = 4), colon cancer (n = 4), gastric cancer (n = 3), and glottis, esophagus, pancreas, and ovary cancer (one each). The median size of the largest metastatic adrenal tumor was 3.5 cm, with a range of 1–10 cm. In 21 patients (65.2%), CRP was elevated (>1 mg/dL), and 12 patients

Table 1 Baseline clinicopathological features of enrolled patients

Variables	
Age (median, range)	63.5 (35–82)
Sex (%)	
Female	5 (15.6)
Male	27 (84.4)
Size of metastasis (cm; median, range)	3.5 (1–10)
Interval: primary diagnosis to adrenalectomy (months; median, range)	8.8 (0–93.8)
Intent to treat (%)	
Palliative	10 (31.3)
Cure	22 (68.8)
Site of primary tumor (%)	
Glottis	1 (3.1)
Esophagus	1 (3.1)
Colon	4 (12.5)
Liver	5 (15.6)
Stomach	3 (9.4)
Kidney	4 (12.5)
Lung	11 (34.4)
Cervix	1 (3.1)
Pancreas	1 (3.1)
Ovary	1 (3.1)
Site of metastasis (%)	
Single	14 (43.8)
Both	5 (15.6)
Adrenal + other site	13 (40.6)
Previous metastasectomy	
No	30 (93.8)
Yes	2 (6.3)
Interval: primary diagnosis to adrenalectomy (%)	
≥6 months (metachronous)	13 (40.6)
<6 months (synchronous)	19 (59.4)
ECOG-PS (%)	
0	5 (15.6)
1	23 (71.9)
2	4 (12.5)
Operative method (%)	
Open	20 (62.5)
Laparoscopic	12 (37.5)
Recurrence after adrenalectomy (%)	
No	12 (37.5)
Yes	20 (62.5)
C-reactive protein (mg/dl,%)	
≤1.0	11 (34.4)
>1	21 (65.2)

Table 1 Baseline clinicopathological features of enrolled patients (Continued)

Albumin (g/dl,%)	
<3.5	12 (37.5)
≥3.5	20 (62.5)
GPS (%)	
0	10 (31.3)
1	11 (34.4)
2	11 (34.4)

(37.5%) were hypoalbuminemic (<3.5 mg/dL). GPS of 0, 1, and 2 were distributed evenly (31.3%, 34.4%, and 34.4%, respectively).

Surgical treatment and recurrence

The selection of surgical technique (open or laparoscopic) depended on the individual surgeon. Laparoscopic ADx was performed using a retroperitoneal approach. There were no complications or mortalities related to ADx. Recurrence after ADx was slightly high (62.5%).

Prognostic factors for RFS and OS

The median OS and RFS after ADx in enrolled patients were 10.4 months (range, 0.5-74.3) and 7.3 months (range, 0.5-74.3) respectively. Univariate analyses of the clinicopathological parameters and RFS and OS are shown in Table 2 and Table 3. In the univariate analysis, ADx for cure was significantly associated with a better OS (HR; 0.30 95% CI: 0.10-0.93, p = 0.038). RFS was not associated with intent to treat (for cure, HR; 0.58, 95% CI: 0.23-1.49, p = 0.265). C-reactive protein (>1 mg/dl) showed a worse effect on RFS (HR; 7.55, 95% CI: 1.69-33.6, p = 0.008) and OS (HR; 5.74, 95% CI: 1.24-26.5, p = 0.025). The GPS (=2), together with C-reactive protein and serum albumin level, showed a worse effect on RFS (HR, 6.47, 95% CI: 1.64-25.3, p = 0.007) and OS (HR; 5.33, 95% CI: 1.09-26.0, p = 0.039). Multivariate regression analysis identified the independent negative prognostic factors for OS and RFS (Tables 2 and 3). The independent negative prognostic factors for OS were synchronous metastasis (HR 3.05, 95% CI 1.07-11.94, p = 0.048) and GPS (HR 6.65, 95% CI 1.25-35.23, p = 0.026). The independent negative prognostic factors for RFS were laparoscopic surgery (HR; 4.68, 95% CI: 1.61-13.61, p = 0.005) and GPS (=2, HR; 11.8, 95% CI: 2.50–55.7, p = 0.002).

Discussion

The adrenal glands are one of the most common sites for metastasis, and the prevalence of isolated adrenal metastasis has increased due to routine surveillance of patients with known malignancy using radiologic examinations based on computed tomography, magnetic

Table 2 Univariate and multivariate analysis of variables affecting RFS

	RFS (univariate analysis)		RFS (multivariate analysis)	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (>63.5 years)	1.84 (0.74-4.63)	0.19		
Sex				
Female	1 (reference)			
Male	0.77 (0.24-2.38)	0.651		
Operative method				
Open	1 (reference)		1 (reference)	
Laparoscopy	1.95 (0.78-4.87)	0.152	4.68 (1.61-13.61)	0.005
Intent to treat				
Palliative	1 (reference)			
Cure	0.58 (0.23-1.49)	0.265		
Synchronous metastasis	1.95 (0.72-5.26)	0.186		
Site of metastasis				
Single	1 (reference)			
Both	0.74 (0.15-3.56)	0.714		
Adrenal + other site	1.02 (0.39-2.60)	0.967		
Site of primary tumor				
Other	1 (reference)			
Liver	0.51 (0.11-2.24)	0.373		
Stomach	0.15 (0.01-1.45)	0.103		
Kidney	0.63 (0.11-3.58)	0.604		
Lung	1.68 (0.57-4.94)	0.346		
Previous metastasectomy				
No	1 (reference)			
Yes	0.33 (0.04-2.55)	0.294		
C-reactive protein (mg/dl)				
≤1.0	1 (reference)			
>1	7.55 (1.69-33.6)	0.008		
Albumin (g/dl)				
≥3.5	1 (reference)			
<3.5	2.03 (0.83-4.93)	0.118		
GPS				
0	1 (reference)		1 (reference)	
1	2.82 (0.73-10.9)	0.132	2.77 (0.61-12.69)	0.189
2	6.47 (1.64-25.3)	0.007	11.80 (2.50-55.70)	0.002
ECOG-PS				
0-1	1 (reference)			
2	2.03 (0.65-6.32)	0.222		

resonance imaging, and positron emission tomography [10,12-14]. Although small studies related to adrenalectomy in the setting of metastasis have reported improved survival, patients with adrenal metastasis are frequently regarded as inoperable and have a poor prognosis [7,10,15]. Prognostic factors and surgical indications

for adrenalectomy have not been clearly defined, and more series related to these patients in this setting are needed.

Previously, Muth et al. reported the indication for adrenalectomy for adrenal metastasis with a consecutive series of 30 patients, and the independent prognostic

Table 3 Univariate and multivariate analysis of variables affecting OS

	OS (univariate analysis)		OS (multivariate analysis)	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (>63.5 years)	1.13 (0.37-3.46)	0.823		
Sex				
Female	1 (reference)			
Male	2.56 (0.33-19.7)	0.367		
Operative method				
Open	1 (reference)			
Laparoscopy	1.81 (0.62-5.29)	0.277		
Intent to treat				
Palliative	1 (reference)			
Cure	0.30 (0.10-0.93)	0.038		
Synchronous metastasis	2.15 (0.68-6.73)	0.187	3.05(1.07-11.94)	0.048
Site of metastasis				
Single	1 (reference)			
Both	0.60 (0.07-5.07)	0.64		
Adrenal + other site	1.19 (0.39-3.61)	0.754		
Site of primary tumor				
Other	1 (reference)			
Liver	0.35 (0.05-2.51)	0.301		
Stomach	0.26 (0.02-2.87)	0.277		
Kidney	0.63 (0.09-4.41)	0.648		
Lung	1.41 (0.34-5.75)	0.626		
Previous metastasectomy				
No	1 (reference)			
Yes	0.04 (0–67.8)	0.397		
C-reactive protein (mg/dl)				
≤1.0	1 (reference)			
>1	5.74 (1.24-26.5)	0.025		
Albumin (g/dl)				
≥3.5	1 (reference)			
<3.5	1.96 (0.68-5.61)	0.2		
GPS				
0	1 (reference)		1 (reference)	
1	3.28 (0.60-17.8)	0.168	2.54 (0.46-14.26)	0.288
2	5.33 (1.09-26.0)	0.039	6.65 (1.25-35.23)	0.026
ECOG-PS				
0-1	1 (reference)			
2	1.81 (0.49-6.62)	0.368		

factors of favorable survival were adrenalectomy for potential cure, no previous metastasis surgery, and tumor type [9]. Vazquez et al. identified synchronous disease, tumor type, size, burden, and site as risk factors for poor prognosis in univariate analysis [10]. More recently, Howell et al. suggested that prognostic factors included synchronous disease, a short disease-free interval (DFI), and lung primary [16].

In our study, the independent negative prognostic factors for overall survival (OS) were synchronous metastasis, and GPS. Synchronous metastasis was also an independent prognostic factor in our study. With regard to synchronous

metastasis, it was explained theoretically that patients with a tumor presenting as a synchronous metastasis growing faster or more aggressively and patients with metachronous disease could be regarded as having more indolent tumors [16]. With regard to the laparoscopic and open approach, the laparoscopic method could be a feasible option even in aggressive tumor because we believe that our study include the more aggressive tumor [17,18]. As mentioned before, synchronous tumor and short disease-free interval are related to more aggressive tumor, and overall survival could reflect the tumor aggressiveness [9,10,16]. Tanvetyanon et al. reported that the median overall survival was shorter (~12 months) for patients with synchronous tumor [8]. In our study, there were 19 synchronous patients (59.4%), and the disease-free interval was 8.8 months. The median overall survival was only 10.5 months. Muth et al. reported nine patients (30%) with synchronous disease, a median DFI of 26 months, and a median survival of 23 months [9]. Howell et al. described 11 synchronous patients (19%), a DFI > 12 months for 39 patients (81%), and an overall median survival of 30 months [16]. Howell et al. preferred open surgery in patients with multi-focal disease and in patients with more aggressive tumor. In our study, more aggressive patients were included, and the laparoscopic approach could be used in those patients in line with results in previous studies. However, additional studies are needed to clarify this point.

In our study, GPS was selected as an independent poor prognostic factor in multivariate analysis. GPS is based on a combination of CRP and albumin and has been evaluated in a variety of cancers, such as renal cancer, breast cancer, non-small cell lung cancer, gastroesophageal cancer, pancreatic cancer, and colorectal cancer [19-24]. CRP is a sensitive marker of systemic inflammation, and elevated CRP concentrations are associated with poorer survival in cancer patients, particularly in patients with advanced disease [25]. The association with elevated CRP levels and a dismal prognosis might reflect the prognostic value of tumor produced interleukin-6, an inducer of CRP production in the liver. Presurgical CRP did correlate significantly with shorter RFS and OS in univariate analysis as like other study. Albumin concentrations reflect both systemic inflammation and the amount of lean tissue [25]. GPS, which is a combination of CRP and albumin levels, reflects the effects of systemic inflammatory response and the process of nutritional decline in advanced cancer [26,27]. However, to our knowledge, there has not been a study to evaluate the prognostic significance in cancer patients with metastatic adrenal lesion. Cancer cachexia and the ECOG performance status have been mentioned as prognostic factors, but ECOG performance status is recognized to be subjective [28,29]. In our study, GPS had a prognostic value superior to that of ECOG-PS. Mcmillan suggested

that the GPS is a simple objective measure that can reflect cancer cachexia and predict outcome in patients with cancer [29]. Furthermore, Lamb et al. reported that an elevated GPS prior to surgery might be a useful prognostic indicator in advanced renal cell carcinoma and may alter the decision for surgery [30]. More research will be needed to validate GPS as a risk factor in cancer patients with adrenal metastasis.

Our study has a number of limitations. The study was hampered by selection bias, and several variables are inter-related because of the retrospective study design. Furthermore, the number of patients was relatively small for multivariate analysis, maybe due to this, there were some discrepancies in the results. Hazard ratio (HR) of both adrenal metastasis was lower than that of single metastasis. Moreover, HR of the presence of previous metastasectomy was lower than no history of previous metastasectomy. In addition, heterogenous tumors are included and malignant potential of primary tumor will be the important factor for OS and RFS. However, the number of each tumor type was not sufficient to assess the prognostic value. Larger cohort study also is needed to find out the prognostic value of the malignant potential of primary tumor.

Finally, our results were expressed with respect to the outcomes of RFS and OS, rather than cancer specific survival (CSS). Future studies of prognostic factors should include CSS as an outcome measure.

Conclusion

In our study, synchronous disease, operation method, and inflammation-based prognostic score were significant prognostic factors for survival associated with adrenalectomy in cancer patients with adrenal metastatic diseases. Synchronous metastasis was also a negative prognostic factor, which is in line with results from a previous study. However, with regard to the operation method, further study is necessary to establish the feasibility of adequate outcomes with a laparoscopic approach in patients with aggressive tumors. GPS appears to be superior to ECOG-PS and could be a simple objective prognostic indicator, but the baseline value of GPS prior to surgery needs to be established in additional studies.

Authors' contributions
SGK participated in the design of the study and performed the statistical analysis. ECH participated in the design of the study, performed the statistical analysis and draft the manuscript. IH, SHK, JGL, SHH, and JEH collected the clinical data. SIJ, TWK, DDK, JJK, and JC made critical revision of the manuscript for important intellectual content. SGK and ECH conceived of the study, and approved the final draft of the manuscript. All authors read and approved the final draft of the manuscript.

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