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ORIGINAL SCIENTIFIC REPORT

Patterns of Use and Short-Term Outcomes of Minimally Invasive Surgery for Malignant Pheochromocytoma: A Population-Level Study

P. Goffredo[1] · M. A. Adam[2] · S. M. Thomas[3] · R. P. Scheri[2] · J. A. Sosa[1,2] · S. A. Roman[2]

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Abstract

Background Malignant pheochromocytoma is rare, and there is a scarcity of data on the use of minimally invasive surgery (MIS) for treatment. The aims of this study were to analyze patterns of use of MIS for malignant pheochromocytoma in the U.S. and compare short-term outcomes to those of open adrenalectomy.

Methods Patients with malignant pheochromocytoma undergoing MIS, including laparoscopy, robotic assisted, laparoscopy converted to open, or open adrenalectomy, were culled from the National Cancer Database, from 1998 to 2011. Data were examined using simple summary statistics, X^2 and student's t tests, Mann–Whitney test, and logistic regression.

Results A total of 36 MIS and 67 open adrenalectomies were identified in 2010–2011. No significant differences were observed between the two treatment groups in demographic characteristics or comorbidities. Preoperative diagnosis of malignancy was made in 52.8 % of MIS and 48.5 % of open patients (p = NS). MIS and open adrenalectomies did not differ with respect to lymph node metastases, vascular invasion, extra-adrenal-extension, and distant metastases (all p = NS). MIS tended to more often be used to perform partial adrenalectomy (38.9 vs. 20.4 % open, $p = 0.061$); surgical margins, 30-day readmission and mortality rates were similar to open adrenalectomy (all p = NS). Tumors removed via MIS were smaller (48.7 vs. 73.3 mm open, $p = 0.003$) and associated with a shorter length of stay.

Conclusions A significant proportion of patients with malignant pheochromocytomas underwent MIS, with short-term outcomes which are comparable to those of open surgery. Further studies focused on long-term survival and recurrence are needed to assess the role of MIS in the management of these rare tumors.

Introduction

Malignant pheochromocytomas are rare catecholamine-secreting cancers deriving from the chromaffin cells of the adrenal medulla [1]. When these tumors develop in extra-adrenal sites, such as the carotid bulb, mediastinum, abdomen, or pelvis, they are named paragangliomas [2]. Malignant behavior is found in approximately 10 % of patients and cannot be assessed solely by histopathological evaluation of the tumor [3]. In order to make a diagnosis of

✉ S. A. Roman
sanziana.roman@duke.edu

1 Duke Clinical Research Institute, Durham, NC, USA

2 Department of Surgery, Duke University Medical Center, Durham, NC, USA

3 Department of Biostatistics, Duke University, Durham, NC, USA

malignant pheochromocytoma, the documentation of locoregional invasion or distant metastases at non-chromaffin sites is required [4, 5].

Management strategies for malignant pheochromocytoma include surgery, pharmacological control of sympathetic symptoms, sometimes external beam radiation, and systemic chemotherapy [6]. The mainstay of treatment, however, remains adrenalectomy or debulking surgery, if complete excision cannot be achieved [7]. Surgical options for adrenalectomy include open surgery, transabdominal laparoscopy, retroperitoneoscopic approaches, and robotic surgery [8–12]. Laparoscopic adrenalectomy currently represents the most common surgical treatment for benign adrenal tumors, given its proven safety and several advantages, such as reduced postoperative pain, shorter length of hospital stay, earlier resumption of oral intake, earlier return to normal life, and better cosmetic results compared to open adrenalectomy [13]. Using minimally invasive approaches to resect malignant adrenal lesions is controversial due to potential compromise of oncologic outcomes, as well as the possible associated risk of peritoneal carcinomatosis or port site metastasis from tumor capsule violation [14–22].

Given the rarity of malignant pheochromocytomas, there is a paucity of data regarding use of minimally invasive techniques for these tumors, and current knowledge is based on case reports only. The aims of the current study were to analyze patterns of use of minimally invasive surgery (MIS) for malignant pheochromocytoma in the United States and compare short-term outcomes of patients who underwent MIS versus open adrenalectomy.

Materials and methods

Data sources and study patients

The National Cancer Database (NCDB) is a joint program of the commission on cancer (CoC) of the American College of Surgeons and the American Cancer Society [23]. It is a nationwide comprehensive oncology outcomes database that collects data from more than 1500 Commission-accredited cancer programs in the United States and Puerto Rico. More than 70 % of all newly diagnosed cancer patients are captured by the NCDB. The NCDB started its activity in 1989, and includes nearly 29 million records of cancer patients across the U.S. Data elements are collected and submitted to the NCDB from CoC-accredited cancer program registries using nationally standardized data item and coding definitions. The NCDB is Health Insurance Portability and Accountability Act (HIPAA) compliant. Patients' data are de-identified, and no identifiers for hospitals or healthcare providers are made available to investigators.

The NCDB participant user file was used to identify all patients diagnosed with malignant pheochromocytoma from 1998 to 2011. This database employs the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) as histology coding reference; code 8700/3 identifies patients with malignant pheochromocytomas [24]. Patients younger than 18 years were excluded. A total of 908 patients were identified from 1998 to 2011. Since surgical approach was recorded in the NCDB only after 2010, only 147 patients were included in our analyses. We then limited our cohort to patients who underwent surgery, obtaining a final N of 103.

Demographic variables of interest were patient gender, age at diagnosis, race, education, annual income, year of diagnosis, geographic areas, insurance status, metropolitan versus non-metropolitan counties, facility type, and distanced travelled by the patient to undergo surgery. Race was recoded into white, black, and other. Education level was estimated by matching the patient's zip code recorded at the time of diagnosis against files derived from year 2000 US Census data, providing a measure of the number of adults in the patient's zip code who did not graduate from high school; it was treated as a binary variable, low (<14 %) or high (≥ 14 %). Annual income was determined by the NCDB by linking patient's zip code to the year 2000 US Census data, and $35,000 was used as a cut point for low versus high income. Metropolitan counties had a population $\geq 250,000$.

Clinical variables included Charlson/Deyo score to evaluate comorbidity, surgery of primary site, surgical approach, preoperative diagnosis of malignancy, surgical margins, radiation, chemotherapy, length of stay, 30-day readmission and mortality rates, and vital status. Biochemical data are not available in the NCDB. Surgery of primary site was recoded as none, partial (local tumor excision, NOS, simple/partial surgical removal of primary site, and surgery stated to be "debulking"), and total. This variable was recoded as none, minimally invasive surgery (robotic assisted, laparoscopic, laparoscopic converted to open), and open adrenalectomy. Anterior and posterior laparoscopic approaches were not differentiated in the NCDB, and were both coded as laparoscopy. Length of stay was measured in days from surgery, and was treated both as a continuous and a binary variable; 3 days was identified as the cutoff. No biochemical or genetic data were captured in the NCDB.

Pathologic variables were tumor size, laterality, vascular invasion, lymph node status, extra-adrenal extension, and distant metastases. Tumors >300 mm were excluded from our size analyses due to the possibility of coding errors. Lymph node status was classified into not examined,

negative, and positive. Site of distant metastases was available in NCDB only after 2010.

Statistical analyses

Demographic, clinical, and pathologic characteristics of patients were described utilizing simple summary statistics; variables of interest were analyzed with X^2 and student's t test, Mann–Whitney test, and logistic regression. Due to the small sample size, multivariate analysis was performed only for type of surgery at the primary tumor site and the length of stay outcome.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software (version 22.0; SPSS Inc., Chicago, IL, USA); all tests were two-sided, and a p value < 0.05 was set for statistical significance. Because NCDB data are publicly available and all patient information is de-identified, this study was granted an exemption from the institutional review board.

Results

Patients' cohort

A total of 908 malignant pheochromocytomas were identified in the NCDB between 1998 and 2011 (Table 1). Fifty-two percent were female, with a mean age at diagnosis of 52.8 years. The majority of individuals diagnosed with malignant pheochromocytomas were white (75.3 %), and 58 % of malignant pheochromocytomas were treated in academic hospitals.

Most of the patients presented with a low Charlson/Deyo score, with 72.9 % scored as 0, 22.3 % as 1, and 4.7 % as $\geq$2. Surgery of the primary site represented a partial adrenalectomy in 24.2 % of cases, and a total adrenalectomy in 52.5; 23.3 % of individuals did not undergo surgery. Among the 147 patients in the cohort with known surgical approach, 29.9 % did not receive surgery, 45.6 % underwent surgery via an open approach, and 21.7 % with MIS. Overall experience with malignant pheochromocytoma is scarce; most institutions performed one laparoscopic adrenalectomy per year, with only two institutions having done two adrenalectomies. Fifty-one percent of patients had a preoperative diagnosis of malignancy. Surgical margins were positive in 15.2 % of patients; 7.2 % were treated with external beam radiation therapy, and 9.4 % received chemotherapy. Mean length of hospital stay was 5.6 days. Nearly 4 % of individuals were readmitted within 30 days from surgery, and 1.9 % died in the same time frame.

Malignant pheochromocytomas had a mean tumor size of 75.6 mm with a standard deviation of 47.3 mm; 50.5 % involved the right adrenal gland, 46.4 % the left adrenal gland, and 3.1 % were bilateral. Vascular invasion was found in 38.8 % of tumors, extra-adrenal extension in 25.8 %, and distant metastases in 25.8 %. Lymph nodes were not examined in 84.1 % of patients; among lymph nodes examined, 50.8 % were positive.

Surgical approach: patient's characteristics and short-term outcomes

A total number of 36 MIS and 67 open adrenalectomies were identified between 2010 and 2011. No difference was observed in the distribution of patient demographic characteristics by surgical approach [p = not significant (NS)] (Table 2). MIS patients had similar comorbidity scores to open adrenalectomy patients: 66.7 versus 71.6 % had a Charlson/Deyo score of 0, and 33.3 versus 28.4 of $\geq$1, respectively (p = NS). A preoperative diagnosis of malignancy was made in 52.8 % of MIS and 48.5 % of open surgery patients (p = NS). There were no reported discrepancies in radiation and chemotherapy rates for either group (p = NS). The two subsets of patients did not differ with respect to the presence of positive lymph nodes (50.0 % MIS vs. 58.3 % open adrenalectomy), the presence of vascular invasion (41.7 vs. 41.2 %), extra-adrenal-extension, and distant metastases (all p = NS). Malignant pheochromocytomas treated with MIS were smaller than those treated with open adrenalectomies (mean = 48.7 vs. 73.3 mm, $p = 0.003$).

Minimally invasive surgery tended to be more often employed for partial adrenalectomy (38.9 vs. 20.4 % open, $p = 0.061$), and, after adjustment for possible confounders, including gender, age, comorbidities score, tumor size and hospital type, an association was confirmed (Odds ratio [OR] 2.79, 95 % Confidence interval [CI] 1.00–7.73, $p = 0.049$). However, number of lymph node harvested, positive surgical margins (OR 2.02, CI 0.60–6.76), 30-day readmission (OR 0.45, CI 0.05–4.19), 30-day mortality rates, and mean length of stay were similar among the two subsets of patients (all p = NS). Nonetheless, median length of stay was shorter in the MIS group (3 vs. 5 days); 57.1 % MIS stayed in the hospital for $\leq$3 days versus 28.3 % open adrenalectomy patients (OR 3.39, CI 1.34–8.56, $p = 0.009$). After adjustment for gender, age, comorbidities score, surgery of primary site, tumor size, and hospital type, MIS was more likely to be associated with a length of stay $\leq$3 days (OR 3.94, CI 1.45–10.74, $p = 0.007$).

Discussion

To the best of our knowledge, this is the largest published series of malignant pheochromocytomas. We describe the demographic, clinical, and pathologic characteristics of

Table 1 Demographic, clinical and pathologic characteristics of patients with malignant pheochromocytoma, NCDB 1998–2011, $n = 908$

	Patient characteristics	Malignant pheochromocytoma	
		n	%
Demographic	Gender		
	Female	475	52.3
	Age at diagnosis, years	52.8 ± 15.3	
	Race ($n = 900$)		
	White	678	75.3
	Black	180	20.0
	Other	42	4.7
	Education ($n = 856$)		
	More educated	283	33.1
	Annual income ($n = 856$)		
	≥$35,000	550	64.3
	Year of diagnosis		
	1998–2004	402	44.3
	2005–2011	506	55.7
	Geographic area		
	North-east	204	22.5
	South	391	43.1
	Midwest	181	19.9
	West	132	14.5
	Insurance ($n = 713$)		
	None	49	6.9
	Private	444	62.3
	Government	220	30.9
	Metro/urban ($n = 860$)		
	Metro	720	83.7
	Urban	126	14.7
	Rural	14	1.6
	Facility type ($n = 897$)		
	Community	64	7.1
	Comprehensive	314	35.0
	Academic	519	57.9
	Distance travelled, miles ($n = 870$)	65.3 ± 190.4	
Clinical	Charlson/Deyo score		
	0	461	72.9
	1	141	22.3
	≥2	30	4.7
	Surgery primary site ($n = 794$)		
	None	185	23.3
	Partial	192	24.2
	Total	417	52.5
	Surgical approach ($n = 147$)		
	None	44	29.9
	Minimally invasive	36	24.4
	Open	67	45.6
	Surgical margins ($n = 514$)		
	Positive	78	15.2
	Preoperative diagnosis of malignancy ($n = 716$)		
	Yes	367	51.3
	Radiation ($n = 877$)		
	None	814	92.8
	External beam radiation therapy	63	7.2
	Chemotherapy ($n = 876$)		
	Yes	82	9.4
	Length of stay		
	Mean ± SD	5.6 ± 5.0	
	Median	5.0	
	Range	1–58	
	30-day readmission ($n = 612$)		
	Yes	22	3.6
	30-day mortality		
	Yes	14	1.9
	Vital status		
	Dead	230	43.6
Pathologic	Tumor size (mm)		
	Mean ± SD	75.6 ± 47.3	
	Median	65.0	
	Range	2–300	
	Laterality ($n = 839$)		
	Right	424	50.5
	Left	389	46.4
	Bilateral	26	3.1
	Vascular invasion ($n = 67$)		
	Yes	26	38.8
	Lymph nodes status ($n = 820$)		
	Not examined	690	84.1
	Examined		
	Negative	64	49.2
	Positive	66	50.8
	Extra-adrenal extension ($n = 625$)		
	Yes	161	25.8
	Distant metastases ($n = 527$)		
	Yes	136	25.8

Percentages have been rounded and may not add up to 100

SD standard deviation

908 patients with this malignancy at a population level. Surgical approach was recorded for 103 patients: 35 % underwent MIS. While there was a 10 % increase in the rate of positive margins for tumors resected laparoscopically, this was not statistically different from open

Table 2 Demographic, clinical, and pathologic characteristics of patients with malignant pheochromocytoma who underwent minimally invasive surgery (MIS, $n = 36$) versus open surgery ($n = 67$), NCDB 2010–2011

	Patient characteristics	Surgery (%)		p value
		MIS	Open	
Demographic	Gender			0.844
	Female	52.8	50.7	
	Age at diagnosis (years)			0.674
	Mean ± SD	54.7 ± 15.4	53.4 ± 13.9	
	Race		$n = 65$	0.636
	White	72.2	67.7	
	Black and other	27.8	32.3	
	Education	$n = 32$	$n = 61$	0.898
	More educated	75.0	73.8	
	Annual income	$n = 32$	$n = 61$	0.905
	≥$35,000	59.4	60.7	
	Geographic area			0.160
	Northeast	34.3	20.3	
	South	34.3	53.1	
	West and Midwest	31.4	26.6	
	Metro county	$n = 32$	$n = 61$	0.431
	Yes	84.4	90.2	
	Distance travelled (miles)	$n = 34$	$n = 62$	0.323
	Mean ± SD	36.0 ± 69.1	75.9 ± 228.1	
	Academic center			0.209
	Yes	61.1	73.1	
	Insurance	$n = 29$	$n = 43$	0.865
	Private	65.5	67.4	
	Government	34.5	32.6	
Clinical	Charlson/Deyo score			0.600
	0	66.7	71.6	
	≥1	33.3	28.4	
	Surgery primary site		$n = 49$	0.061
	Partial	38.9	20.4	
	Total	61.1	79.6	
	Preoperative diagnosis of malignancy		$n = 66$	0.679
	Yes	52.8	48.5	
	Surgical margins	$n = 29$	$n = 44$	0.251
	Positive	≤35.0[a]	≤23.0[a]	
	Radiation			0.461
	None	100.0	98.5	
	Chemotherapy	$n = 35$	$n = 65$	0.471
	None	92.1	93.8	
	Length of stay, continuous	$n = 35$	$n = 46$	0.350
	Mean ± SD	4.3 ± 4.1	5.1 ± 3.3	
	Median	3.0	5.0	
	Range	0–18	0–15	
	Length of stay >3 days	$n = 35$	$n = 46$	0.009
	Yes	42.9	71.7	
	30-day readmission			0.472
	Yes	≤28.0[a]	≤15.0[a]	

Table 2 continued

	Patient characteristics	Surgery (%)		*p* value
		MIS	Open	
	30-day mortality			0.295
	Yes	0.0	≤ 14.0[a]	
Pathologic	Tumor size (mm)	*n* = 35	*n* = 51	0.003
	Mean ± SD	48.7 ± 24.1	73.3 ± 42.9	
	Median	50.0	66.0	
	Range	13–107	14–210	
	Laterality	*n* = 35	*n* = 66	0.665
	Right	48.6	53.1	
	Left	51.4	46.9	
	Vascular invasion	*n* = 24	*n* = 34	0.970
	Yes	41.7	41.2	
	Lymph nodes status		*n* = 66	0.622
	Not examined	88.9	81.8	
	Examined			0.549
	Mean ± SD	5.3 ± 7.5	8.6 ± 13.0	
	Range	1–14	1–44	
	Extra-adrenal extension	*n* = 32	*n* = 66	0.679
	Yes	≤32.0[a]	24.2	
	Distant metastases			0.657
	Yes	≤28.0[a]	≤15.0[a]	

Where not else indicated MIS $n = 36$, open $n = 67$

SD standard deviation

[a] Per NCDB policy, the exact value of cells <10 cannot be reported

adrenalectomy. Compared to open adrenalectomy, there was no observed difference in the number of lymph nodes harvested, 30-day mortality or readmission rates, while length of stay was shorter in the MIS group. Malignant pheochromocytomas treated with MIS were significantly smaller than those managed with an open approach.

A previous population-based study of 287 malignant pheochromocytomas diagnosed between 1988 and 2008 in the surveillance, epidemiology, and end results (SEER) database investigated predictors of overall mortality [25]. The 5-year overall survival rate was 58.1 %; presentation at diagnosis with distant metastases and failure to undergo surgery were factors independently associated with compromised survival. Demographic, clinical, and pathologic characteristics of patients with malignant pheochromocytomas were similar to those reported here from the NCDB database, lending credence to our observations.

Toniato analyzed 25 patients with malignant adrenal tumors diagnosed between 1991 and 2010; nine of these had primary adrenocortical carcinomas and 16 had adrenal metastases [15]. Laparoscopic adrenalectomy was successfully performed in 16.6 and 93.3 % of the patients, respectively. The authors concluded that laparoscopic resection was inappropriate for patients with adrenocortical carcinoma, whereas adrenal metastases may undergo a minimally invasive approach. Sroka et al. retrospectively studied 121 laparoscopic adrenalectomies performed from 2003 to 2011 [16]. A total of 11 primary malignancies (five adrenocortical carcinoma, five large B cell lymphoma, and one leiomyosarcoma) and ten metastatic lesions were included. No conversion to laparotomy was necessary, and MIS for primary or metastatic malignant lesions was deemed to be feasible and oncologically safe. In 2008, McCaulet et al. performed a review of the literature to evaluate the role of laparoscopy in managing adrenal malignancies [18]. After analyzing 11 series reported from 2002 to 2008, they concluded that selected patients may undergo laparoscopic adrenalectomy for malignancy with equal oncologic outcomes to open approaches and less postoperative morbidity. In the medical literature, there is clearly a lack of data regarding the use of MIS for malignant pheochromocytomas. Several authors have investigated the use of minimally invasive and open surgery for the treatment of adrenal primaries and/or metastases, but there are no studies to date focusing on malignant pheochromocytomas. We analyzed 36 patients who

underwent MIS and found that short-term outcomes were equivalent to those of patients managed with open surgery; nonetheless, data regarding long-term oncologic outcomes are not currently available in the NCDB, and, thus, remain to be investigated.

In 2008, Parnaby et al. published a series of 111 adrenalectomies performed between 1999 and 2006: 101 laparoscopic and ten open. Thirty-nine percent of MIS and 90 % of open surgeries were for neoplasms ≥6 cm [19]. The authors described comparable operative and oncologic outcomes from minimally invasive adrenalectomy for patients with neoplasms ≥6 cm to those of individuals with lesions <6 cm when local invasion was not present. They concluded that an initial laparoscopic approach for noninvasive adrenal tumors can be employed safely. Similar conclusions were supported by Conzo et al. after retrospectively reviewing 88 consecutive patients who underwent laparoscopic adrenalectomy for adrenal malignancy or benign tumors between 2003 and 2013 [26]. Nevertheless, size may represent an obstacle to the feasibility of MIS in adrenal lesions, particularly in the setting of malignant disease, where rupture of the capsule increases the likelihood of persistent and recurrent disease [27]. We observed a smaller mean tumor size in the NCDB for MIS malignant pheochromocytomas, suggesting that overall adrenal surgeons appear to use good judgment when they decide to perform minimally invasive adrenal surgery for pheochromocytomas that in the end are malignant.

Limitations of the current study include those inherent to studies based on large databases, such as the potential for coding errors. However, data reporting to the NCDB are highly standardized and heavily audited [28]. Given the fact that the database does not capture information on survival after 2006 and disease recurrence, these could not be included in our analyses. Biochemical data and genetic/familial disease status are not available in the NCDB, and could not be analyzed. Since surgical approach was recorded since 2010, only 2 years of data were included in the analyses. We could not separately analyze each of the MIS methods (robotic assisted, laparoscopic, and laparoscopic converted to open). Despite representing the largest series of malignant pheochromocytomas reported in the medical literature, this study may still be underpowered to capture all significant differences between MIS and open adrenalectomy.

In summary, the current study analyzes the largest cohort of patients diagnosed with malignant pheochromocytoma who have undergone MIS. We found comparable short-term outcomes between minimally invasive and open adrenalectomy, although minimally invasive surgery was performed for tumors that were smaller, on average. It appears that MIS might be employed in a select subset of patients; further studies on long-term outcomes, including disease-specific survival and recurrence, are needed before the routine use of MIS can be advocated for the management of this malignancy.

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Conflict of interest The authors have no financial conflict of interest. The data used in the study are derived from a de-identified National Cancer Data Base (NCDB) file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

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