Summary of clinical characteristics of common primary adrenal malignancies in adults

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Research

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Abstract

Background

To summary the clinical characteristics of common primary adrenal malignancies in adults, the survival time of the patients, and the prognostic factors associated with these rare malignancies.

Methods

The Surveillance, Epidemiology, and End Results database (1975–2016) was queried for all patients who were diagnosed with primary adrenal malignancies, including adrenocortical carcinoma(ACC), pheochromocytoma and paraganglioma (PPGL), lymphoma, and sarcoma (SA). The clinical characteristics, overall survival (OS) and cancer-specific survival (CSS) were analyzed, in which propensity score methodology, logistic regression modeling and Kaplan-Meier survival curves were used. The Multivariate Cox proportional hazard model was used to identify factors affecting the prognosis of patients with ACC.

Results

3204 patients with primary adrenal malignancies were identified, including 2180 with ACC, 593 with PPGL, 307 with lymphoma, and 124 with SA. Generally, PPGL had a better prognosis than others. For ACC and PPGL, the non-metastatic group had better OS and CSS than the metastatic group; for SA, the non-metastatic group had better OS, however, there was no significant difference in CSS between the two groups. Furthermore, For ACC, the single metastasis group had a better OS than the multiple metastasis group. After tumors metastasis, the surgery group, surgery of primary adrenal lesions, had better OS and CSS than the non-surgery group for ACC and PPGL. For lymphoma, the chemotherapy group had better OS and CSS; for ACC and PPGL, the chemotherapy group had better CSS and worse OS; for SA, the survival showed no significant difference between the two groups. Radiotherapy had the same effect on patients' survival as chemotherapy, except for the lymphoma and the ACC. As for lymphoma, the radiotherapy group had better CSS, whereas the survival showed no significant difference in OS between the two groups. For ACC, the non-radiotherapy group had better CSS and OS. More importantly, for lymphoma, under the condition that both cohorts were the same basically, the surgical group had a better prognosis. The prognosis of ACC was related to sex, age, seer historic stage, surgery, chemotherapy.

Conclusion

Understanding the clinical characteristics of these tumors and factors affecting prognosis can facilitate the selection of more appropriate clinical treatment options.

Introduction

Adrenal incidentalomas (AIs) were an asymptomatic mass greater than 1 cm in diameter[1] discovered incidentally on medical imagelogy performed for diseases except for adrenal disease[2], and its prevalence increased with age[3]. Among all adrenal tumors, the non-functioning benign lesion was the most common, followed by cortisol secreting adenoma, pheochromocytoma, adrenocortical carcinoma, metastatic lesion, and aldosteronoma[4].

From 5–10% of the adrenal incidentalomas were true malignancies[5, 6], furthermore, in patients with known cancer, from 50–75% of adrenal incidentalomas may be metastatic disease[1, 7]. So we can find the fact that primary adrenal malignancies were relatively rare. Even with studies of primary adrenal malignancies, it was only explored in isolation[8–13]. It seemed primary adrenal malignancies had rarely been studied as a whole. Therefore, the clinical characteristics of common primary adrenal malignancies in adults, the survival time of the patients, and the impact of related factors on survival time were explored together in the study.

In the present study, the common primary adrenal malignancies in adults were adrenocortical carcinoma (ACC), pheochromocytomas, and paraganglioma (PPGL), lymphoma, and sarcoma (SA). The survival time, including overall survival (OS) and cancer-specific survival (CSS), was analyzed. Moreover, the survival time was explored according to relevant influencing factors. By using the Surveillance, Epidemiology, and End Results (SEER) database, the clinical data of 3204 patients were collected and analyzed to provide a basis for appropriate treatments of these tumors.

Materials And Methods

Patients with a primary adrenal malignancy diagnosed between 1975 and 2016 were identified; the analysis limited to 4 common histologic types (ACC, PPGL, lymphoma, SA), was performed. Based on the SEER registry, age at diagnosis, sex, and race were included in the demographic variable. Tumor size, tumor grade, disease laterality, radiation, chemotherapy, SEER historic stage (distant, regional, and localized), and survival months were included in the clinical variables.

Statistical Analysis

SPSS 22.0 software was used for statistical analysis. In the case of skewed distribution and categorical data, the data use the rank-sum test. Kaplan-Meier survival curves were generated to evaluate CSS and OS. To adjust for the selection bias inherent in the analysis, we used the propensity score methodology.

When the effect of surgery on survival of patients with metastatic adrenal primary cancer was studied, the following variables for patients were selected to calculate the propensity score: age, sex, race, radiotherapy, chemotherapy, stage, grade, metastasis (single or multiple). Furthermore, this variable, metastasis, was deleted when studying the effect of single and multiple metastases on the survival of patients with ACC. Moreover, when it came to the effect of surgery on survival in patients with lymphoma, the variable, distant metastases were added. As for the radiotherapy and chemotherapy, the variables, age, sex, race, stage, grade, seer historic stage, were selected to calculate the propensity score.

In patients with primary adrenal malignancies, propensity scores were computed by logistic regression modeling. In our propensity analyses, a 1:1 matching ratio was used. For patients with ACC, the multivariate Cox proportional hazard model was used to identify factors affecting their prognosis. A *P*-value of < 0.05 was considered statistically significant for all tests.

Results

The clinical characteristics of common primary adrenal malignancies in adults were shown in Table 1. 3204 patients with primary adrenal malignancies were identified, including 2180 with ACC, 593 with PPGL, 307 with lymphoma, and 124 with SA. Some obvious features in certain types of these malignancies were observed in the present study. The mean age of patients with lymphoma (69.91 years) and sarcoma (62.63 years) was higher than those with ACC and PPGL (mean age, 52.46, and 51.11 years, respectively). The tumor with the largest mean diameter was found to be SA (11.74 cm), followed by ACC (11.68 cm), PPGL (8.34 cm), lymphoma (5.0 cm). Compared to those with ACC (0.9%), PPGL (1.3%) and SA (2.4%), patients with lymphoma (32.2%) had more bilateral lesions. Surgery was performed in patients with ACC, PPGL, and SA (51.8%, 55.6%, and 60.5%, respectively), whereas the chemotherapy was the primary mode of treatment for patients with lymphoma (65.8%). Radiotherapy was rarely used for these tumors. Patients who had ACC (38.1%), PPGL (38.8%), and SA (37.1%) presented with the localized disease; in the 3 cohorts, patients with distant disease tended to be the patients with ACC.

Figure 1 depicted the OS and CSS of each histologic subtype; generally, the prognosis of these tumors was different (*P* = 0.00), furthermore, PPGL had a better prognosis relatively.

Survival time was compared between the metastatic and non-metastatic groups for each type of tumor in Figure 2. The prognosis of patients with ACC without metastases was better than the metastatic group (*P*os = 0.00, *P*css = 0.00), as which PPGL was same (*P*os = 0.00, *P*css = 0.011). For SA, the non-metastatic group had better OS (*P*os = 0.00), however, there was no significant difference in CSS between the two groups (*P*css = 0.08). As we can see from Figure 6, regarding ACC, the single metastasis group had a better OS than the multiple metastasis group (*P*os = 0.002). Figure 3 illustrated the comparison of OS and CSS between the surgical group and the non-surgical group after these malignancies metastasis. The surgical group had better OS and CSS than non-surgical group for ACC (*P*os = 0.00, *P*css = 0.00). For the patients with PPGL, the surgical group had better CSS (*P*css = 0.008), whereas there was no significant difference in OS between the two groups (*P*os = 0.571).

The comparison of OS and CSS between the chemotherapy group and the non-chemotherapy group for the four types of tumors was shown in Figure 4. For lymphoma, the chemotherapy group had better OS and CSS (*P*os = 0.026, *P*css = 0.00); for ACC and PPGL, the chemotherapy group had better CSS and worse OS (*P*os = 0.00, *P*css = 0.00). In terms of SA, survival showed no significant difference between groups. Radiotherapy had the same effect on the survival of patients with PPGL and SA as chemotherapy. For lymphoma, the radiotherapy group had better CSS (*P*css = 0.003), whereas the survival showed no significant difference in OS between two groups (*P*os = 0.085, Figure 5). For ACC, the non- radiotherapy group had better CSS and OS.

The survival outcomes of lymphoma were analyzed in Figure 7. The prognosis of surgical group was better than the non-surgical group (*P*os = 0.003, *P*css = 0.004).

Finally, by using the proportional risk model, we identified factors affecting the prognosis of the patient with ACC, accounting for the available demographic and clinical characteristics. In general, women, older age, seer historic stage were taken into account as risk factors for the patients. In detail, higher risk can be seen in women (HR, 1.224; *P*css = 0.031) and older age (HR, 1.007; *P*css = 0.021). As for seer historic stage, region group vs local group; HR, 2.197; *P*css = 0.00 and distant group vs local group; HR, 2.839; *P*css = 0.00 had more risk. On the contrary, surgery (vs the non-surgery; HR, 0.432; *P*css = 0.00) and chemotherapy (vs the non-chemotherapy; HR, 0.665; *P*css = 0.00) were considered to be protective factors.

Discussion

With the wide use of imaging techniques, there was an increasing number of AIs. Some studies thought AIs may be a clinically valuable biomarker because AIs were associated with a distinctly increased incidence of malignancies and higher mortality[14]. Most AIs were benign, but a few were functional and malignant[15]. As for distinguishing malignant tumors from benign tumors, the size of 46 mm was of great value, with a sensitivity of 88.2% and specificity of 95.5%[16]. The primary adrenal malignancies were divided into 5 histologic groups: adrenocortical carcinomas, pheochromocytomas and paragangliomas, neuroblastomas, non-Hodgkin lymphomas, and sarcomas[17]. However, according to clinical experience, the common primary adrenal malignancies in adults mainly included adrenocortical carcinoma (ACC), pheochromocytomas and paraganglioma (PPGL), lymphoma, and sarcoma (SA).

In the present study, among patients with four tumors, those with PPGL had better survival. Whereas, according to our clinical impression, lymphoma had a better prognosis due to chemotherapy, which was different from our results, possibly because of multiple classifications of lymphoma. The OS for ACC was poor, meanwhile, it was previously mentioned that the 5-year survival rate fluctuated between 32% and 50% for patients with resectable tumors and the median survival was less than 1 year for those with metastatic disease[18]. Of course, the prognosis of these tumors was related to metastasis, surgery, chemotherapy, radiotherapy, and other factors.

In general, the non-metastatic group had better OS and CSS for patients with malignant tumors. In our study, for patients with ACC and PPGL, the non-metastatic had better OS and CSS. Poor survival was associated with synchronous metastasis, which can be seen in patients with PPGL[19–22]. Whereas for patients with SA, the non-metastatic group had a better OS, but there was no significant difference in CSS between the two groups. We can further speculate that sarcoma was different from ACC and PPGL in terms of disease nature. Tumor metastasis was not a qualitative leap for the disease progression of sarcoma, which may be because sarcoma progresses rapidly. It was noted that, for ACC, compared with the multiple metastasis group, the single metastasis group had better OS. The lymphoma was excluded because of a limited number of events.

The metastasis group was divided into the surgical group and the non-surgical group, furthermore, the survival comparison of two groups was performed. As for the metastatic carcinoma, one study indicated

that primary site surgery in metastatic ACC patients significantly improved OS and CSS[23], which had been confirmed in our research. Complete resection for metastatic foci and systemic therapy may improve outcomes in patients with stage IV ACC[24]. For patients with metastatic paraganglioma, primary tumor resection appeared to be associated with improved OS[25]. However, in our study, surgery didn't improve the patients' OS but it did improve the patient's CSS.

On the whole, currently available therapeutic options mainly include surgical excision, radiotherapy, chemotherapy, and targeted therapy. It was important to note that primary adrenal lymphoma was rare, accounting for < 1% of non-Hodgkin lymphomas, furthermore, the most common category was diffuse large B cell lymphoma (DLBCL)[26–28], which was the same as our outcome. There was still no consensus on the treatment of primary adrenal lymphoma. Some authors had used a combination of surgery and chemotherapy[29]. While ensuring multiple variables comparable with propensity score methodology, patients who had undergone surgery had a better prognosis than the non-surgical group in the present study. Similarly, surgery played a significant role in the management of malignant PPGL. Surgical excision can bring durable survival for patients with malignant PPGL[30]. For patients with ACC, surgery can offer a 25% chance of actual 5-year survival and a 7% chance of actual 10-year survival. Furthermore, the accurate pre-operative staging was important to select an appropriate surgical strategy. For large and potentially invasive ACC, multi-organ resection remained the preferentially selected approach; a more extensive resection was needed by patients with smaller ACC[31]. Based on our previous discussion, we can conclude that for the patient with ACC, surgical resection of the primary tumor can offer improved survival, irrespective of disease stage[32]. For patients with SA, surgical resection for initial debulking and local control of tumors with adjuvant chemotherapy and radiotherapy can have a better outcomes[33, 34].

The clinical results of adjuvant therapy have been disappointing. Some indicated adjuvant radiotherapy may prolong the time to ACC local recurrence[35, 36], some even thought adjuvant therapy was associated with decreased recurrence[24], others suggested it was of benefit in stage IV disease[32, 37]. However, there was a consensus that it was no benefit for OS[24, 35, 38]. In our study, patients receiving adjuvant therapy didn't have significantly improved OS. Whereas, the chemotherapy group had better CSS and worse OS. We hypothesized that chemotherapy would be useful for ACC and prolong the survival of patients. But OS was not improved due to gastrointestinal and neurologic toxicity. Targeted therapy was gradually recognized, whereas its clinical effect was also unsatisfactory[39, 40]. This may be due to the multiple molecular pathways involved in the pathogenesis of ACC, which may make different drug classes effective in only a small subgroup of patients.

By contrast, radiation therapy was a useful treatment for malignant PPGL, and higher radiation therapy dose was associated with improved local control[41]. I-131-metaiodobenzylguanidine (MIBG) was the only approved therapy in the US for patients with metastatic PPGL[42]. However, compared to I-131-MIBG therapy, peptide receptor radionuclide therapy had logistic and radiation-safety advantages[43]. As for the chemotherapy, the combination chemotherapy cyclophosphamide, vincristine, and dacarbazine (CVD) was recommended to be considered part of the initial management in patients with metastatic succinate dehydrogenase complex subunit B (SDHB)-related PPGL, because cyclical CVD chemotherapy lead to

continued tumor reduction of metastatic PPGL harboring SDHB mutations[44]. Meanwhile, in our results, adjuvant therapy, radiotherapy, and chemotherapy can improve the CSS of the patients with PPGL. In patients with metastatic PPGL, ablative therapy and interferon-alpha were gradually used to prolong the time of disease stabilizations[45, 46].

It should be highlighted that radiotherapy and chemotherapy were of benefit to the survival of patients with lymphoma, whereas there was no significant difference between the radiotherapy group and the non-radiotherapy group in OS. Compared to the patients without any other treatments, patients with chemotherapy had a superior OS and CSS[47], which was the same as our study. More specifically, rituximab combined with intrathecal methotrexate was effective against adrenal lymphomas[48]. However, the OS was still despite polychemotherapy[49]. As mentioned earlier, SA had historically been managed with a combination of surgery, chemotherapy, and radiotherapy. However, chemoradiotherapy had no significant effect on the survival of patients with SA in our study, which may be due to varieties of SA.

At last, the impact of related factors on survival time was explored together in the study, including age at diagnosis, gender, grade, stage, chemotherapy, metastasis, and type of treatment. Generally, among these factors, the tumor stage had a dominant effect[50–52]. So patients with ACC identified incidentally had improved survival compared with the patients presented with symptoms[53]. Similarly, the seer historic stage had an important influence on the outcome in our study. In the aspect of metastasis and chemotherapy, some studies presented the presence of lymphatic metastasis was an unfavorable prognostic factor, while postoperative therapy with mitotane was a protective prognostic factor for survival in patients with ACC[54]. Some researchers even suggested that mitotane treatment may be associated with better outcomes regardless of the tumor stage[55]. At the same time, our study showed that patients without metastasis had better OS and CSS. In patients having metastasis, patients with single metastasis had a better OS than patients with multiple metastases.

Furthermore, based on advancing research, pathological markers such as the Ki67 index were also important prognostic indicators for ACC[37, 40, 55]. What's more interesting was that the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) might be new biomarkers for predicting the prognosis of adrenal tumor patients. The higher NLR group (NLR $\geq$ 5) showed a significantly poorer OS[56], whereas preoperative LMR greater than 4 were associated with longer CSS[57].

Our research had some specific limitations. Although the number of cases in the SEER database was sufficient, the number of specific cases having full data was insufficient due to the defect in the database itself. Therefore, there may be some bias in the evaluation of results.

Conclusion

Understanding the clinical characteristics of common primary adrenal malignancies in adults was found to be of great significance for accurately evaluating them and selecting the most suitable treatment.

Declarations

Ethics approval and consent to participate

The name of the ethics committee: Ethics Committee of First Affiliated Hospital of Dalian Medical University

The ethics office of our hospital believes that ethical approval of this article is unnecessary

Availability of data and material

The data came from the SEER database

Competing interests

The authors do not have any possible conflicts of interest.

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Article topic design: Deyong Yang

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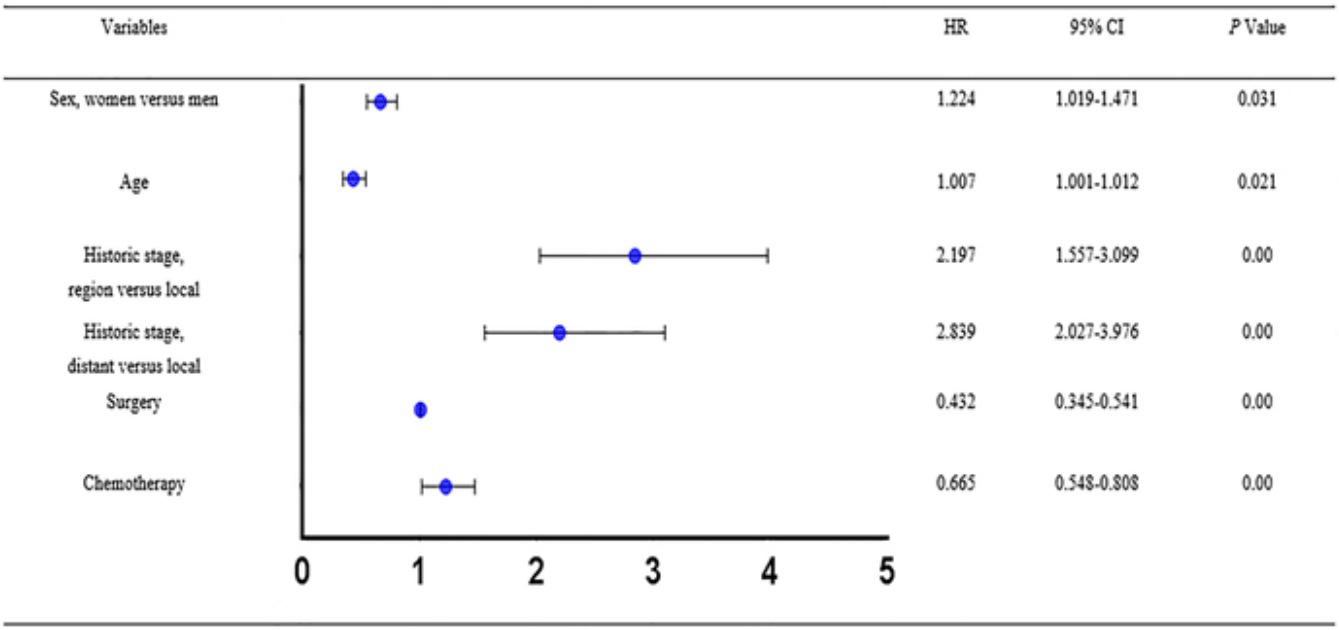
Tables

Table1. Comparison of the clinical features of primary adrenal malignancies in adults

		No. of Patients				
characteristic		Adrenocortical Carcinoma	Pheochromocytoma and Paraganglioma	Lymphoma	Sarcoma	P Value
Total no.		2180	593	307	124	
Sex	male	921	301	199	61	0.00
	female	1259	292	108	63	
Age（mean）		52.46	51.11	69.91	62.63	0.00
Size（cm）		11.68	8.34	5.0	11.74	0.00
Location	left	1127	264	124	60	0.00
	right	960	263	77	61	
	bila	19	8	99	3	
Stage		28	0	28	0	0.00
		173	0	27	0	
		80	0	6	0	
		290	0	35	0	
Grade		65	3	1	4	0.00
		87	1	1	13	
		171	11	2	12	
		120	5	5	30	
Lymphatic metastasis	yes	73	7	0	3	0.00
	no	1018	287	13	71	
Distant metastases	Yes	441	89	1	14	0.00
	no	701	212	12	60	
Single metastasis		16	3	1	1	
Multiple metastasis		97	16	0	0	
Surgery	yes	1130	330	49	75	0.00
	no	440	121	215	31	
Radition	yes	276	54	28	25	0.001
	no	1904	539	279	99	

Chemotherapy	yes	716	49	202	29	0.00
	no	1464	544	105	95	
SEER historic stage	localized	830	230	10	46	0.00
	regional	433	107	5	27	
	distant	813	154	5	33	

Table 2. Multivariate Cox proportional hazard model for CSS in patients with ACC



Figures

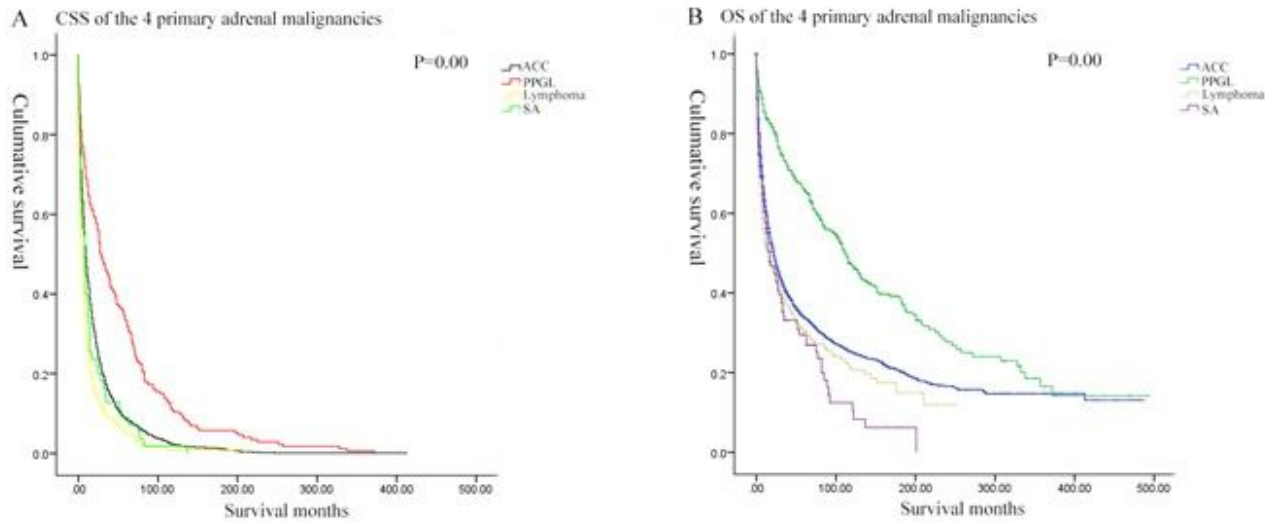


Figure 1

Overall survival (OS) and Cancer-specific survival (CSS) of the 4 primary adrenal malignancies

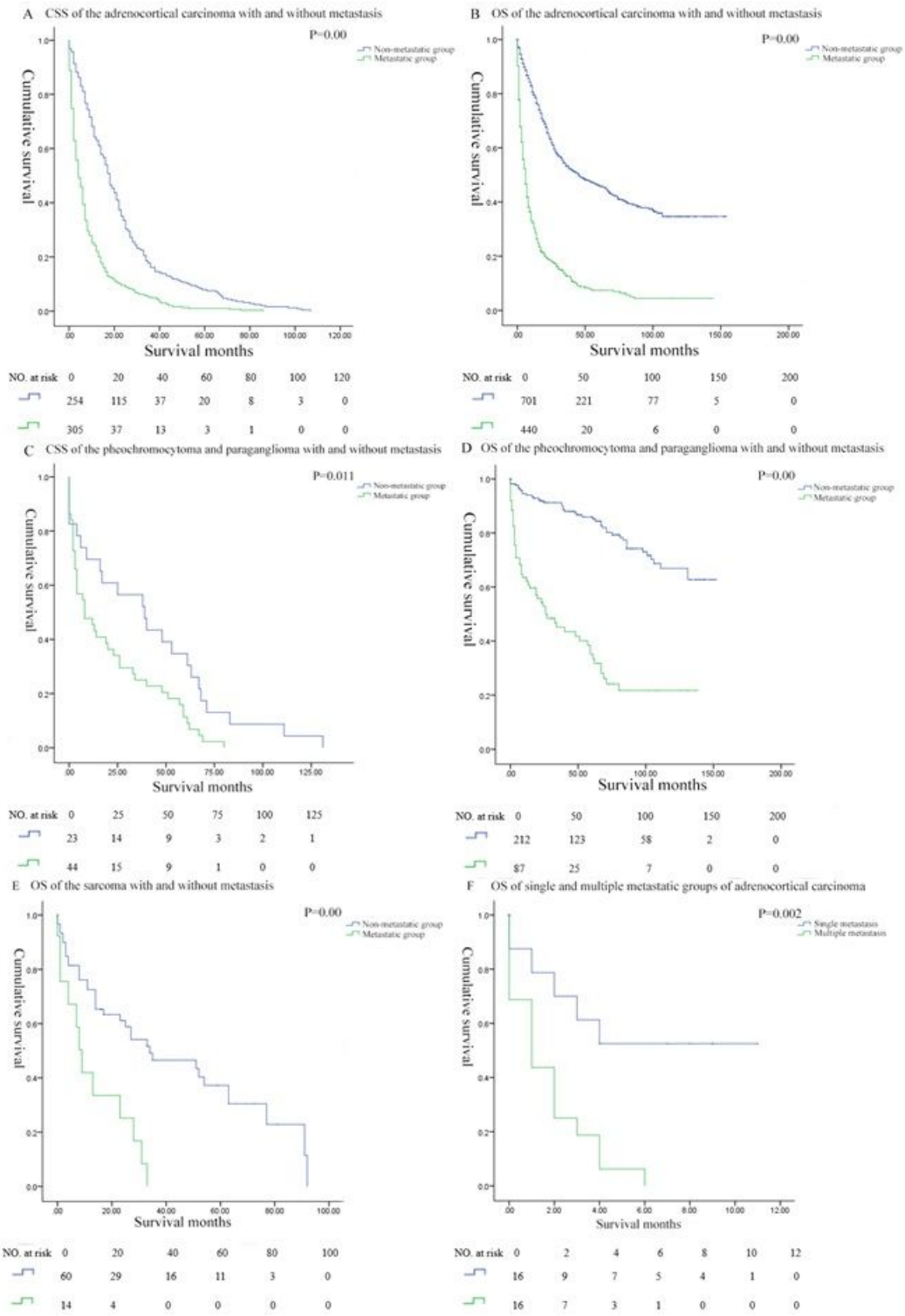


Figure 2

Cancer-specific survival (CSS) and Overall survival (OS) of the 3 primary adrenal malignancies with and without metastasis

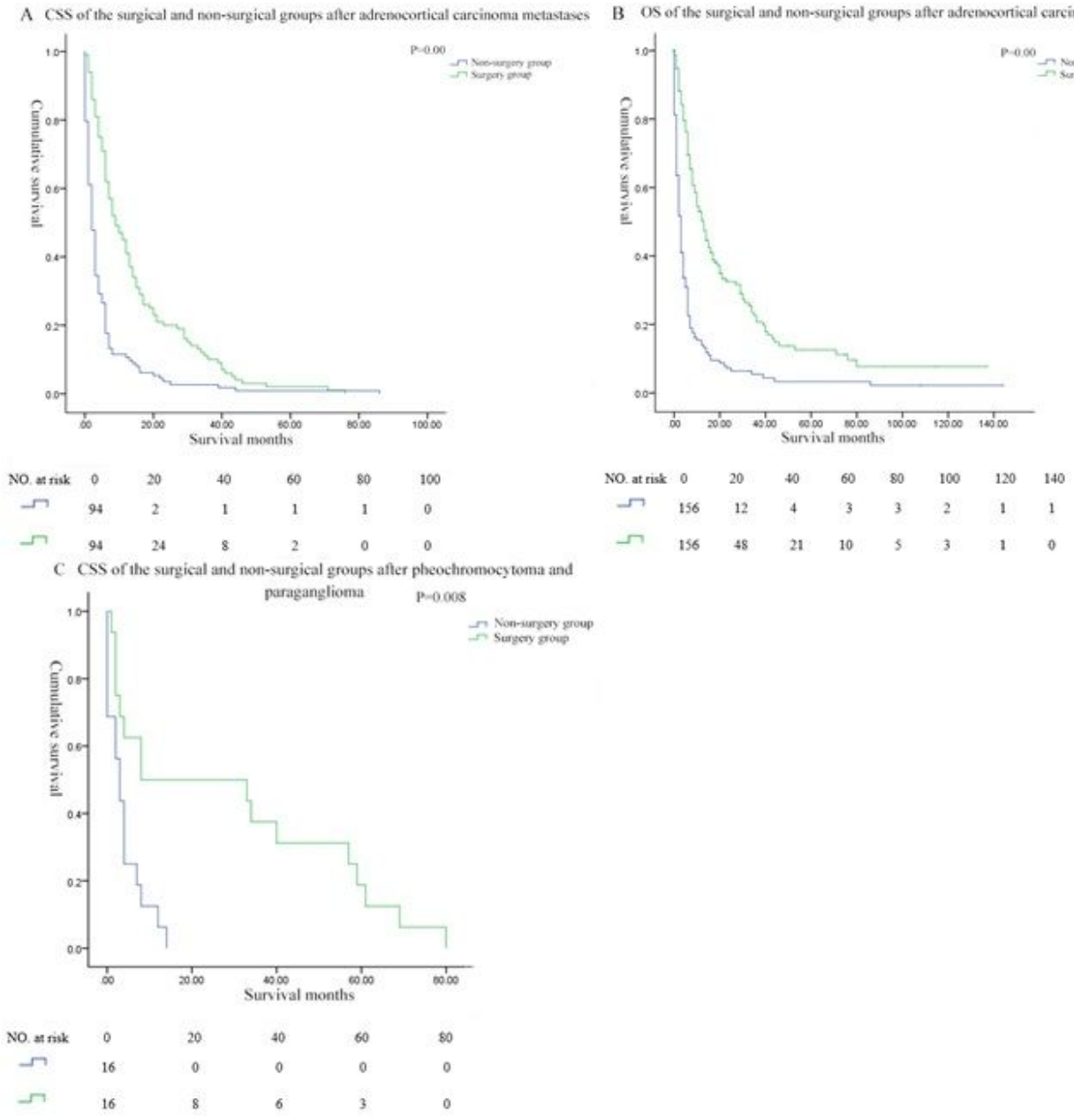


Figure 3

Cancer-specific survival (CSS) and Overall survival (OS) of the surgical and non-surgical groups after three tumors metastases

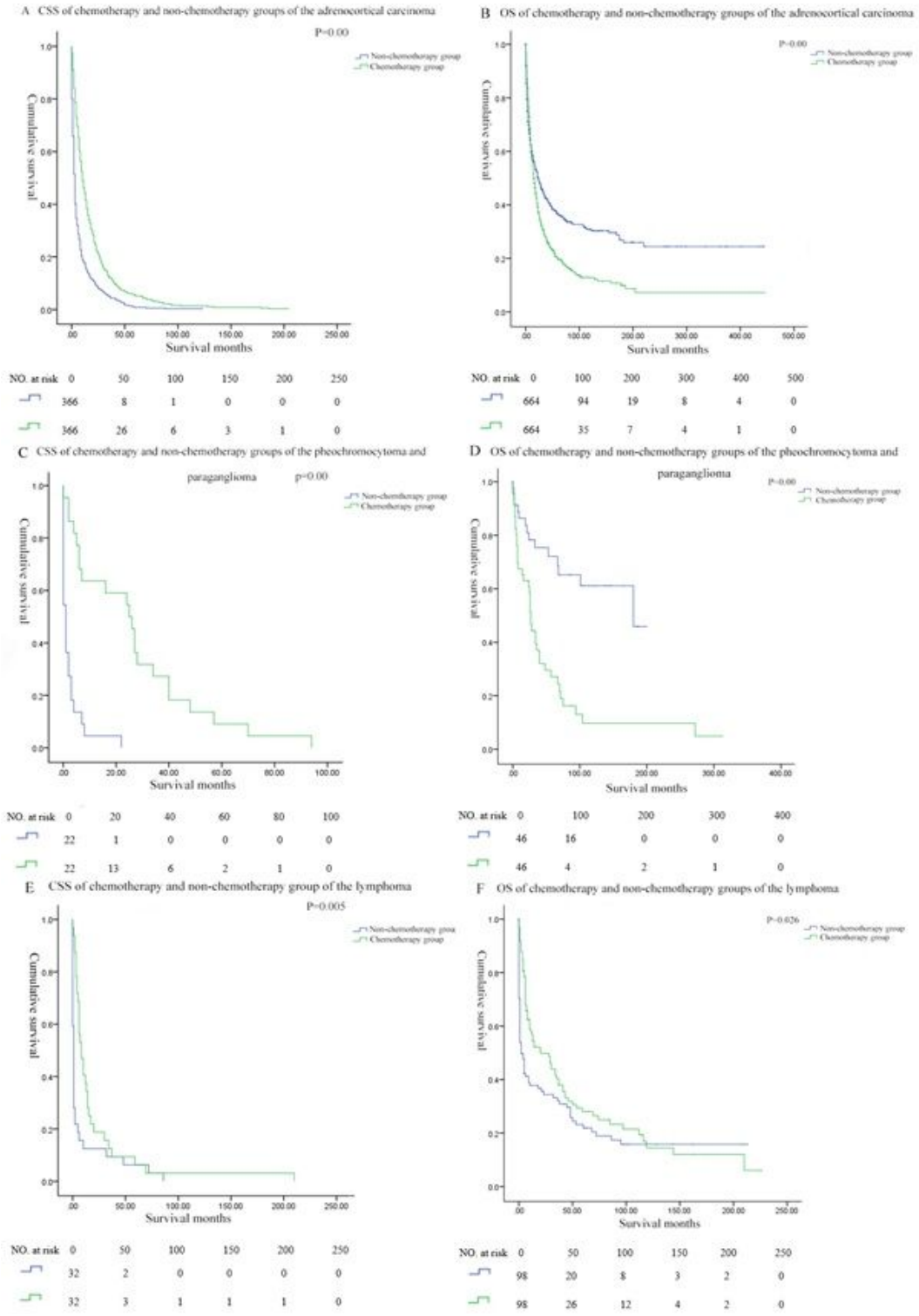


Figure 4

Cancer-specific survival (CSS) and Overall survival (OS) of chemotherapy and non-chemotherapy groups of the 4 primary adrenal malignancie

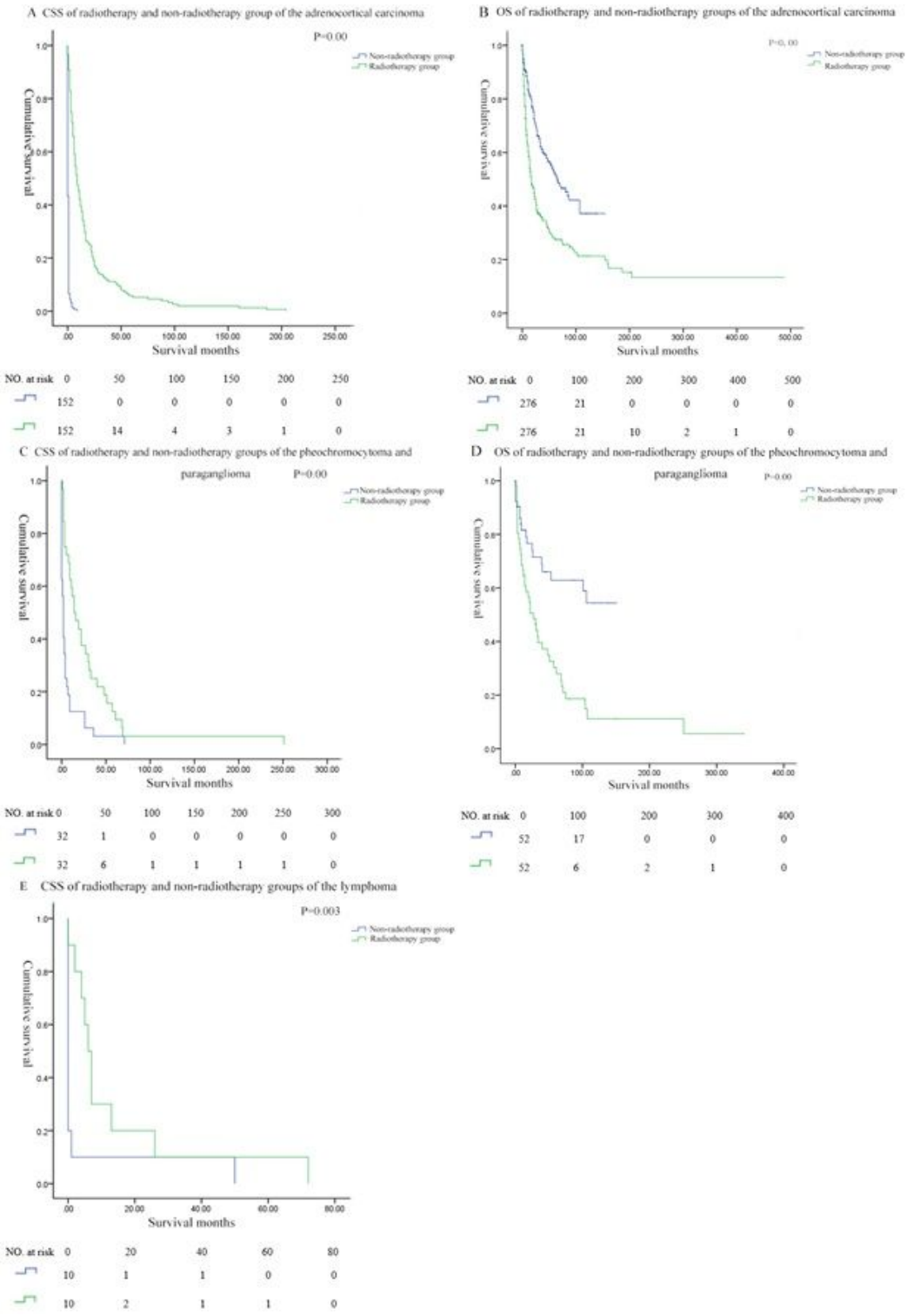


Figure 5

Cancer-specific survival (CSS) and Overall survival (OS) of radiotherapy and non-radiotherapy groups of the 4 primary adrenal malignancie

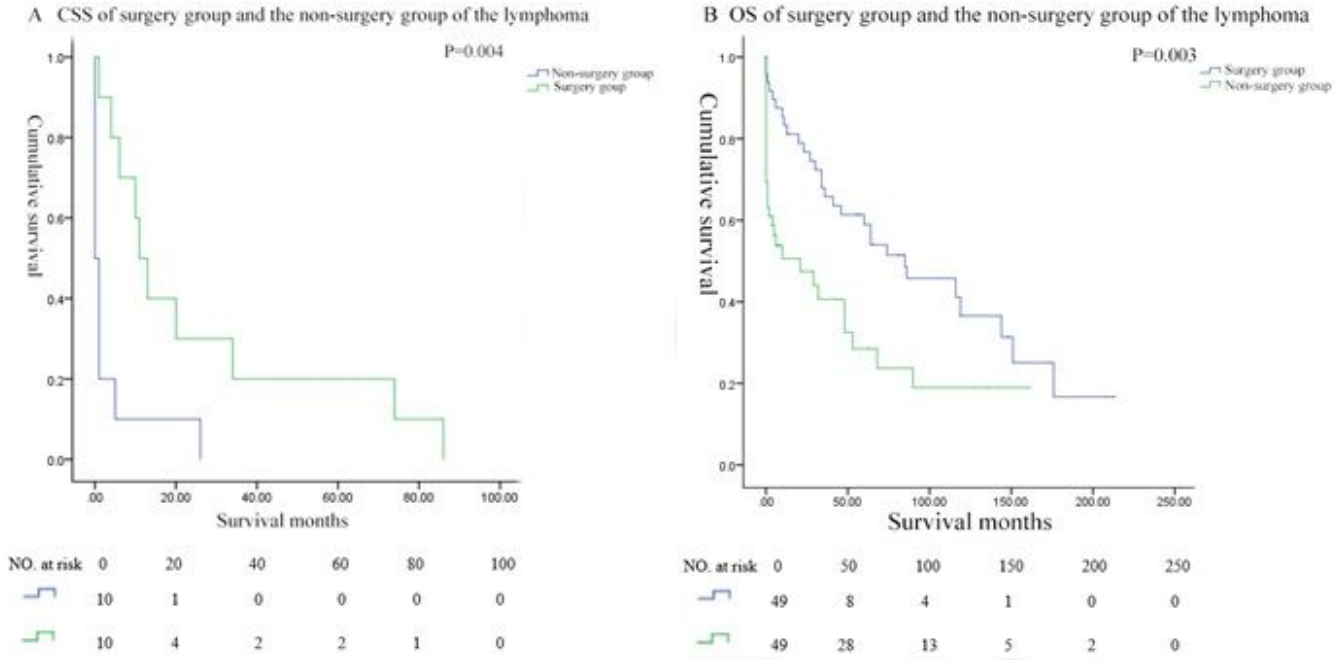


Figure 6

Cancer-specific survival (CSS) and Overall survival (OS) of surgery group and the non-surgery group of the lymphoma