Adrenal ganglioneuroblastoma with metastasis near the renal hilum in an adult female: A case report and review of the literature

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Abstract. Ganglioneuroblastoma (GNB), predominantly observed in children, is an uncommon malignant tumor in adults, with established treatment protocols notably lacking. The present study details the case of a 20-year-old woman who presented with a left adrenal gland mass, identified during a physical examination. Additionally, an unidentified mass was noted near the renal hilum in the preoperative evaluation. Following thorough preoperative preparation, both the primary adrenal gland mass and the renal hilar mass were surgically removed. The procedure concluded successfully. Pathological analysis confirmed that the left adrenal mass was a GNB and identified the renal hilar mass as a metastatic extension. Postoperative examination revealed a new formation at the original surgical site, later verified as a postoperative scar. Through the publication of a case report and extensive literature review, the present study aims to enhance our understanding of this condition, providing valuable diagnostic, therapeutic and post-recovery references for this rare adult disease.

Introduction

Peripheral neuroblastic tumors (pNTs) are malignant neoplasms originating from multipotential sympathetic neuroblasts, which themselves differentiate from embryonic primitive neural crest cells. These tumors are predominantly located along the sympathetic nervous tract. Classification of pNTs, based on the ratio of Schwann cells to neuroblasts and the extent of cellular maturation and differentiation, includes neuroblastoma (NB), ganglioneuroblastoma (GNB) and ganglioneuroma (GN) (1). GNB is comprised of elements of both malignant NBs and benign GNs, meaning that it has intermediate malignant potential (2). GNB features intermediate cell types with varying degrees of maturation, reflecting the biological heterogeneity of pNTs and their differentiation and maturation capabilities. The pathogenesis of GNB is commonly attributed to the abnormal development, maturation or regression of primitive neural crest cells or neuroblasts (3). GNBs are very rare, with an incidence of ~0.5 cases per 100,000 individuals in the pediatric population. In the adult population, the incidence of GNB is even rarer, with <0.01 cases per 100,000 individuals (4). The clinical symptoms are non-specific, complicating the preoperative diagnosis, and the definitive diagnosis relies on the postoperative pathological examination (5).

The present study reports the case of an adult female diagnosed with left adrenal GNB, accompanied by metastasis near the renal hilum. To enhance comprehension of this rare tumor, a comprehensive literature review was also conducted, focusing on the clinical manifestations and pathological features of GNB, and summarizing the current knowledge on its diagnosis, treatment and prognosis. The study aims to offer valuable insights for the effective understanding and management of this uncommon condition.

Case report

A 20-year-old woman, with no prior history of disease, presented with the incidental discovery of a left adrenal mass during a routine physical examination in September 2022 at The First People's Hospital of Yunnan Province (Kunming, China). A computed tomography (CT) scan revealed an oval, soft-tissue density shadow in the left splenorenal space, ~5.7x4.1 cm in size. The mass exhibited mild arterial phase enhancement and persistent venous phase enhancement, with heterogeneous contrast (Fig. 1A). Initially, the radiologist diagnosed it as a left adrenal gland adenoma. The patient's overall health was

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satisfactory, and a comprehensive physical examination was otherwise normal. Laboratory tests indicated plasma catecholamines levels as follows: 3-methoxytyramine, <0.08 nmol/l (normal reference, <0.18 nmol/l); methoxyadrenaline, 0.12 nmol/l (normal reference, ≤0.5 nmol/l); and methoxynorepinephrine, 0.3 nmol/l (normal reference, ≤0.9 nmol/l). A 24-h urine specimen revealed the following: Methoxyadrenaline, 118 nmol/24 h (normal reference, <216 nmol/l/24 h); methoxynorepinephrine, 179 nmol/24 h (normal reference, <312 nmol/l/24 h); 3-methoxytyramine, 413 nmol/24 h (normal reference, <382 nmol/l/24 h); and urinary cortisol, 32.9 μg/24 h (normal reference, 3.5-45 μg/24 h). In a standing and supine position, whole-body blood analysis showed renin at 99.8 (normal reference, 4.0-38.0) and 15.0 pg/ml (normal reference, 4.0-24.0 pg/ml), respectively, adrenocorticotropic hormone at 15.052 and 31.276 pg/ml (normal reference, 7.200-63.400 pg/ml), respectively, cortisol at 15.008 and 18.108 μg/dl (normal reference, 4.260-24.850 μg/dl), respectively, and aldosterone at 275.173 pg/ml (normal reference, 40.000-310.000 pg/ml) and 114.743 pg/ml (normal reference, 10.000-160.000 pg/ml), respectively. The adrenal function tests were within normal limits, except for an elevated 24-h urinary 3-methoxytyramine level and standing plasma renin concentration. Liver and kidney function tests showed total protein at 60.9 g/l (normal reference, 65-85 g/l) and globulin at 19.9 g/l (normal reference, 20-40 g/l), both slightly below normal, and uric acid at 420 μmol/l (normal reference, 178-416 μmol/l), slightly above normal. Among the tumor markers, the carbohydrate antigen 72-4 level was 8.93 U/ml (normal reference, 0.0-6.9 U/ml). The urinary routine indicator urinary biliogen was measured at 34 μmol/l, which was marginally elevated. Other parameters such as blood routine, electrolyte level and coagulation function were within the normal ranges. For enhanced preoperative planning, a three-dimensional reconstruction of the preoperative mass area was performed. This process unexpectedly revealed a small-diameter mass near the renal hilum and adjacent to the left renal artery (Fig. 2A and B), suggesting a potential metastasis from the primary tumor. However, the proximity of the two masses did not eliminate the possibility of multiple separate tumors, thereby challenging the initial adenoma diagnosis.

Following meticulous preoperative planning and preparation, a laparoscopic resection of the left adrenal tumor was executed. Intraoperative observations corroborated the prior assessment of tumor metastasis. Leveraging the insights from the preoperative three-dimensional reconstruction, both the primary adrenal mass and the adjacent renal hilum mass were successfully excised. The perioperative period was uneventful with no complications. Postoperative pathological evaluation confirmed the renal hilum mass as a metastatic lesion originating from the adrenal GNB. The excised tumor was bifurcated for analysis. The adrenal mass presented as an oval, solid entity with an intact capsule, measuring ~7 cm in diameter. The tumor adjacent to the renal hilum was a round mass, ~1.5 cm in diameter. Neither section exhibited nodules or bleeding, displaying a grayish-yellow hue, with a slightly lobulated appearance (Fig. 2C and D). Histopathology and immunohistochemistry affirmed the diagnosis as intermixed GNB (Fig. 3). For histopathology, the specimens were fixed in 10% formalin solution for 14 h at room temperature (22-30˚C). Embedding was performed in paraffin, and sections were cut to a thickness of 4 μm. Hematoxylin (10-30 min) and eosin (1-3 min) were used as stains, at room temperature. Observations were made using a light microscope (CX43; Olympus Corporation), with a magnification of x40. For immunohistochemical analysis, paraffin-embedded tissue sections were fixed in 10% formalin solution at room temperature for 14-18 h and sectioned at a 4-μm thickness. Synapsin (Syn) and glial fibrillary acidic protein (GFAP) were highlighted as representative in immunohistochemistry. The polymer method was employed to block endogenous HRP activity, with a 3% hydrogen peroxide solution applied for 10 min prior to primary antibody application to eliminate endogenous activity. The primary antibody for Syn (cat. no. MAB-0742; Fuzhou Maixin Biotech Co., Ltd.) was used as supplied and incubated at 25˚C for 60 min. DAB staining revealed the cytoplasmic localization of the target antigen as brown, with nuclei counterstained blue with hematoxylin. GFAP (cat. no. MAB-0769; Fuzhou Maixin Biotech Co., Ltd.) and Syn antibodies were also used for cytoplasmic staining. Observations were made using a light microscope (CX43), with a magnification of x100. The gross tumor specimen exhibited a partial capsule with a gray-white to gray-yellow, slightly firm texture, without visible tumor nodules. Immunohistochemical and hematoxylin and eosin (H&E) staining revealed neuroblastic components positive for neurofilament proteins and Nestin, with varying expression levels of Syn, CgA, CD56 and S-100, while GFAP was negative. The presence of Nestin-positive ganglion cells and Schwannian stroma expressing S-100 was noted. Under H&E staining, neuroblastic components did not form nodular structures, displaying a diffuse and small nested distribution. Ganglion cells and Schwannian stroma (>50%) were interspersed within. These findings led to the diagnosis of GNB intermixed type.

At 3 months post-discharge, the patient returned for a follow-up and a residual oval soft-tissue density shadow, ~3.5x2.0 cm, was detected by CT in the area of the initial surgery (Fig. 1B). This finding raised the possibility of recurrence. Consequently, a follow-up positron emission tomography/CT scan was conducted, which indicated that recurrence of the aforementioned mass could not be discounted, although there was no evidence of systemic metastasis (Fig. 1C). Following internal discussions, it was deduced that while tumor recurrence could not be entirely excluded, the likelihood of scar encapsulation within the surgical area was plausible. To refine this assessment, the opinion of an external expert in pediatric tumors was sought through a national multicenter consultation. The expert's opinion leaned towards postoperative changes and advised close monitoring. The patient underwent further follow-ups at 7 and 12 months post-surgery, during which the mass progressively diminished in size (Fig. 1D and E), corroborating the initial assessment. Consequently, no recurrence or metastasis of the mass was observed during the 1-year postoperative period. In the second year post-surgery, it was recommended that the patient undergo follow-up examinations every 3 months, and subsequently, every 6 months. The patient's most recent follow-up revealed no discomfort, indicating a good recovery.

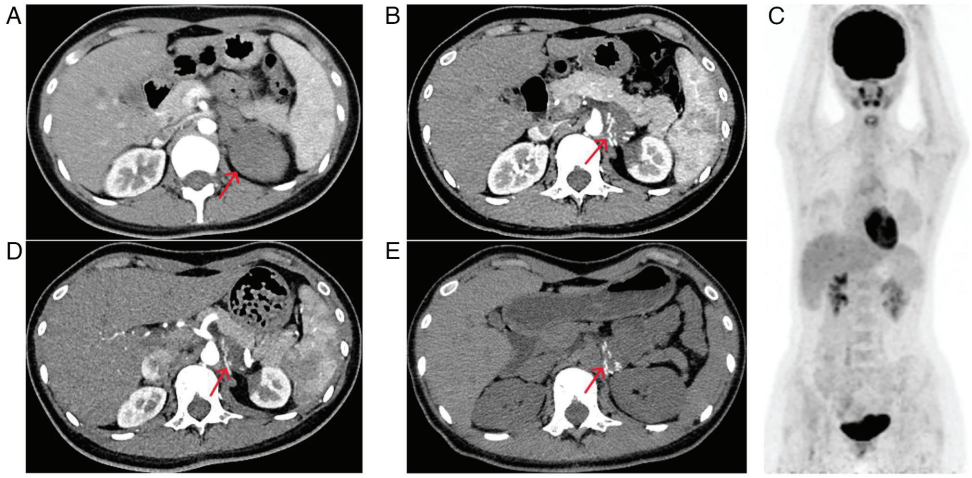

Figure 1. Imaging at admission and follow-up. (A) Arterial phase imaging revealed a solid mass in the left adrenal gland, measuring ~5.7x4.1 cm in maximum diameter. (B) Imaging at 3 months post-surgery indicated a solid mass in the region of the initial surgery, now measuring ~3.5x2.0 cm, suggesting the possibility of recurrence. (C) positron emission tomography-computed tomography scans at 4 months post-surgery showed no evidence of metastasis throughout the body. (D) Postoperative imaging at 7 months demonstrated a reduction in mass size compared with earlier findings, with a maximum diameter of ~2.6x2.0 cm. (E) At the 12-month follow-up, the mass exhibited further shrinkage, with a maximum diameter of ~2.6x1.8 cm. Red arrows indicate the mass.

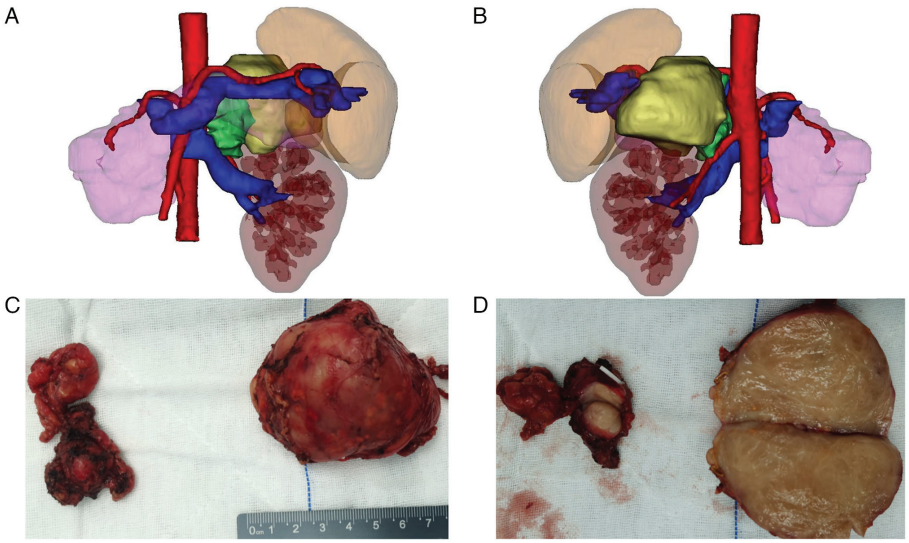

Figure 2. Tumor specimen and preoperative three-dimensional reconstruction. (A) Anterior view of the three-dimensional reconstruction of the mass area: The yellow solid mass represents the primary tumor and the green solid mass indicates metastasis; the orange, brown and purple translucent sections represent the spleen, kidneys and pancreas, respectively; the red and blue sections correspond to the arteries and veins, respectively. (B) The posterior view demonstrates the close proximity of the metastasis to the left renal artery. (C) The excised left adrenal tumor specimen measured ~7 cm in diameter. (D) Both sections of the tumor exhibited no evident nodules or bleeding, presenting with a grayish-yellow, slightly lobulated appearance.

Literature review

Previous reviews of the literature (6,7) reported ~50 cases of adult GNB. However, a search in the PubMed database (www.pubmed.ncbi.nlm.nih.gov/?db=PubMed) using the terms 'ganglioneuroblastoma' or 'GNB' combined with 'adult' yielded data inconsistent with these reports, particularly regarding basic information and case numbers. Data were modified and reorganized, excluding cases where patients were younger than 18 years at the onset of the disease, had significant missing clinical information or had mixed-type tumors, resulting in the identification of 104 cases of adult GNB (4,6-78) (Table I). The demographic breakdown included 54 males and 50 females, yielding a male-to-female ratio of 1.08:1. The mean age of the patients was 37.8 years (range, 19-88 years), with a median age of 34 years. The tumors appeared in various anatomical locations, with abdominal and pelvic involvement in 50 cases (48%), for which the adrenal glands were the most common site (29/50; 58%). This distribution, with a nearly equal male-to-female ratio (15:14), aligns with recent findings by Stevens *et al* (79), but contrasts with those in the studies by Bolzacchini *et al* (66) and Vassallo *et al* (77), which reported a male predominance in adult adrenal GNB. Following the adrenal glands, other common sites included the retroperitoneum, abdomen, kidneys, pelvis, small intestine and ovaries. The intrathoracic cavity was another frequent location for adult GNB (23/104; 22%), predominantly the mediastinum. GNB in the central nervous system accounted for 19% of cases

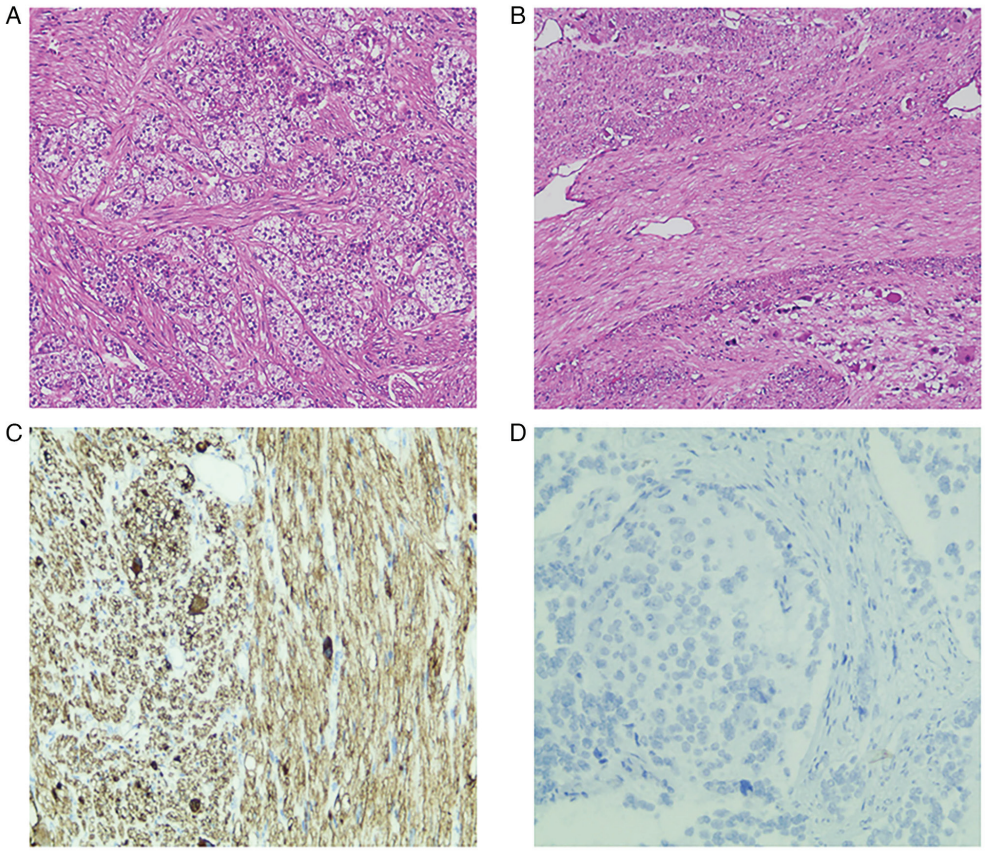

Figure 3. Pathological and immunohistochemical analysis post-surgical resection. (A) Neuroblast nests, varying in differentiation, were interspersed with fibrous vessels. Tumor cells exhibited either eosinophilic or weakly eosinophilic cytoplasm, enlarged nuclei, pale-stained nuclei, prominent nucleoli and focal Homer-Wright rosettes. Some cells were small and round with deeply stained, small nuclei and scant cytoplasm (hematoxylin and eosin; magnification, x40). (B) A diffuse or clustered arrangement of differentiated, mature ganglion cells was observed among proliferating small round cells and spindle-shaped stroma (hematoxylin and eosin; magnification, x40). (C) Immunohistochemical staining showed synapsin positivity (magnification, x100). (D) Immunohistochemical staining indicated glial fibrillary acidic protein negativity (magnification, x100).

(20/104), most commonly affecting the brain and spinal cord. Additional rare sites included the neck (3/104; 3%), bones (3/104; 3%), parotid glands (2/104; 2%) and nose (2/104; 2%). Distant metastases were noted in 27 cases (26%), with localized infiltration in 15 cases (14%), indicating that ~40% (42/104) of patients experienced metastasis or dissemination. This finding corresponds with the research of LaBrosse *et al* (80). However, Schipper *et al* (7) reported a slightly higher incidence of metastasis or localized infiltration (56%) and purely localized infiltration (20%) in a study of 50 GNB cases.

Data analysis in the present study was performed using the R language (R Core Team), with a threshold of $P<0.05$ set for statistical significance. The analysis focused on the association between seven clinicopathological factors and OS in patients, and concentrating on those with complete follow-up data. Survival analysis was conducted using the Kaplan-Meier method, with differences between categories within same groups assessed using the log-rank test. The results indicated that factors such as patient sex, age, tumor size, primary tumor location, tumor pathology type and treatment regimen did not exhibit a statistically significant impact on OS (Fig. 4). However, the presence of local infiltration or distant metastasis was identified as a critical factor influencing OS rates ($P=0.017$) (Fig. 5). While traditional classification systems and several studies have categorized GNBn as having a poor prognosis and GNBi as having a favorable prognosis (81-83), the present analysis revealed that the effect of different tumor pathology types on OS in adult patients was not significant. Given the importance of tumor infiltration and distant metastasis in determining patient OS, further analysis was conducted using χ^2 tests and Fisher's exact probability tests. This analysis assessed the relationship between these outcomes and five clinicopathological characteristics (Table II). The findings showed that tumor infiltration and metastasis were not associated with the patient's sex, age, tumor size or tumor pathological type, but were significantly associated with the anatomical location of the tumor ($P=0.017$) (Table II). The highest incidence of infiltration and metastasis was found in tumors situated in the abdominal cavity and pelvis, excluding the adrenal gland (12/16; 75%). By contrast, the infiltration and metastasis rates for adrenal and intrathoracic tumors were both at 50% (11/22; 8/16), with the lowest incidence observed in central nervous system tumors (2/13; 15%).

Discussion

pNTs represent the most prevalent category of extracranial neoplasms in children, originating from the primitive neural crest. The International Neuroblastoma Pathology Committee revised the International Neuroblastoma Pathology

Table I. Clinicopathological and therapeutic data of 104 cases of GNB obtained from the literature.

First author, year	Sex	Age, years	Sites	Size, cm	Metastasis	Initial treatment	Outcome (months)	Symptoms	Histopathology	(Refs.)
Busch *et al*, 1928	F	30	Retroperitoneal	NA	Liver	RT	DOD (36)	NA	NA	(43)[a]
Crile *et al*, 1929	F	40	Neck	NA	None	Surg	DOD (several)	NA	NA	(43)[a]
Hackel, 1930	F	43	Ganglion	NA	NA	NA	DOD (6)	NA	NA	(43)[a]
Lewis *et al*, 1930	M	41	Neck	NA	Lung	Surg	DOD (several)	NA	NA	(43)[a]
Schaffner *et al*, 1937	M	35	Mediastinum	7.6	None	Surg	NA	Horner's syndrome	NA	(8)
Butz, 1940	M	25	Adrenal	NA	Liver, LN	NA	NA	NA	NA	(43)[a]
Bosse *et al*, 1944	M	88	Neck	5	None	Surg	DOD (1)	Neck mass	NA	(43)[a]
Ackerman *et al*, 1951	M	23	Posterior mediastinum	NA	Local	NA	DOD (3.5)	Chest pain	NA	(9)
Gondos and Reingold, 1964	M	66	Posterior mediastinum	12	Multiple metastases	RT + ChT	DOD (15)	Chest pain	NA	(10)
Cameron *et al*, 1967	F	54	Adrenal	NA	None	Surg	NED (42)	Diarrhea	NA	(11)
Telleschi, 1971	F	72	Nasal fossa	NA	Local	RT	NA	NA	NA	(43)[a]
Nyaradi *et al*, 1971	F	63	Retroperitoneal	NA	None	Surg	Alive (3)	NA	NA	(43)[a]
Kilton *et al*, 1976	F	30	Paravertebral	9	LN, vein	Surg + RT	DOD (10)	Lumbar pain	NA	(12)
	M	62	Retroperitoneal	12	Marrow, bone	ChT	DOD (7)	Lumbar pain	NA	
Knapp and Ruebner, 1976	M	30	NA	NA	Liver, LN	Surg	DOD (114)	Upper abdominal pain	NA	(13)
Feigin and Cohen, 1977	M	27	Adrenal	4	Brain, cerebellum	NA	DOD (0)	Faint	NA	(14)
Taylor *et al*, 1977	M	50	Adrenal	9	NA	Surg	NA	Diarrhea	NA	(15)
Mannes *et al*, 1979	F	28	Abdominal	NA	Bone, lung, LN	ChT	NA	Lumbar pain	NA	(16)
Lopez *et al*, 1980	F	33	Abdominal	NA	Multiple metastases	Surg + ChT	AWD (23)	Left upper abdominal mass	NA	(43)[a]
	F	44	Abdominal	NA	Liver, kidney	Surg + ChT	Alive (22)	Right upper abdominal mass	NA	
Zajtchuk *et al*, 1980	F	22	Thorax	NA	NA	Surg + RT	NED (48)	NA	NA	(17)
	M	29	Thorax	NA	NA	Surg + RT	NED (108)	NA	NA	
Adam and Hochholzer, 1981	M	29	Posterior mediastinum	NA	Local	Surg + RT	AWD (168)	NA	NA	(18)
	F	34	Posterior mediastinum	NA	None	Surg + RT	NED (8)	NA	NA	
	F	39	Posterior mediastinum	NA	None	Surg + RT	NED (96)	NA	NA	
Cooney, 1981	M	47	Lung	4.5	None	Surg	NED (35)	Cough	NA	(19)
Pearl *et al*, 1981	M	27	Brain	3	NA	Surg + RT	DOD (70)	Epileptic	NA	(20)
Li *et al*, 1982	M	50	Thorax	32	None	Surg	Alive (48)	Cough	NA	(21)
Hosaka *et al*, 1982	M	19	Skull base	NA	None	Surg + RT	AWD (96)	Visual impairment	NA	(22)
Nakajima *et al*, 1983	F	36	Brain	NA	None	Surg + RT	NED (39)	Convulsion	NA	(23)
Barr *et al*, 1986	F	26	Small bowel	2.5	LN	Surg	NED (18)	NA	NA	(24)
Slaats *et al*, 1987	F	31	Mediastinum	NA	Remote	Surg + ChT	DOD (20)	NA	NA	(43)[a]
Takahashi *et al*, 1988	M	21	Adrenal	8.8	LN	Surg + ChT + RT	NED (8)	Abdominal pain	NA	(25)
Jalleh *et al*, 1990	F	68	Kidney	20	Liver	NA	DOD (1)	Lumbar mass	NA	(26)
Koido *et al*, 1991	F	39	Retroperitoneal	6	None	Surg	Alive (36)	NA	NA	(43)[a]
Katoh *et al*, 1990-1991	M	69	Retroperitoneal	NA	None	Surg + ChT	Alive (6)	NA	NA	(43)[a]
Roberston *et al*, 1991	M	30	Mediastinum	NA	Local	Surg	AWD (7)	Abdominal pain	NA	(27)

Table I. Continued.

First author, year	Sex	Age, years	Sites	Size, cm	Metastasis	Initial treatment	Outcome (months)	Symptoms	Histopathology	(Refs.)
Koizumi *et al*, 1992	F	47	Adrenal	9	Marrow	NA	DOD (3)	Lumbar pain	NA	(28)
Roberts *et al*, 1992	F	23	Adrenal	25	None	Surg	NED (24)	Right hypochondrium discomfort, hypertension	NA	(29)
Higuchi *et al*, 1993	M	29	Adrenal	11	Bone	Surg + ChT	AWD (10)	NA	NA	(43)[a]
Raina *et al*, 1993	M	21	Spinal cord	3	Local	ChT	NED (24)	Lumbar pain	NA	(30)
Fujii *et al*, 1994	M	50	Nasal cavity	NA	Local	RT + ChT	Alive (8)	NA	NA	(43)[a]
Sibilla *et al*, 1995	M	42	Spinal cord	NA	Local	Surg	AWD (3)	Right lower extremity weakness	NA	(31)
Hiroshige *et al*, 1995	M	35	Adrenal	10	None	Surg	NED (24)	Asymptomatic	NA	(32)
Asada *et al*, 1996	F	61	Thymus	4	NA	Surg	NA	Weakness	NA	(33)
Mehta *et al*, 1997	M	22	Adrenal	9	NA	Surg	NA	Abdominal mass	NA	(34)
Nagashima *et al*, 1997	M	79	Anterior mediastinum	8	None	Surg + ChT	NED (60)	Chest pain	NA	(35)
Hochholzer *et al*, 1998	F	38	Lung	3	Local	NA	DOD (0)	Digestive tract symptom (hormone secretion)	NA	(36)
	F	20	Lung	5	None	Surg	NED (12)	Asymptomatic	NA	
Rousseau *et al*, 1998	F	NA	Adrenal	NA	Liver	Surg + RT + ChT	NA	NA	NA	(37)
Tanaka *et al*, 1998	M	57	Pineal	3	None	Surg + RT	Alive (15)	NA	NA	(7)
Tripathy *et al*, 2000	F	39	Spinal cord	NA	None	Surg	NED (6)	Lumbar pain	NA	(38)
Freeman and Otis, 2001	F	59	Lung	3	None	Surg	NA	NA	NA	(39)
Yamanaka *et al*, 2001	M	60	Retroperitoneal	16	LN	Surg	NED (3), suicide (8)	Asymptomatic	NA	(40)
Tanaka *et al*, 2002	M	63	Mediastinum	NA	NA	NA	NA	NA	NA	(41)
Slapa *et al*, 2002	F	20	Adrenal	18	None	Surg	NED (12)	Asymptomatic	NA	(42)
Koike *et al*, 2003	M	50	Adrenal	4.5	NA	Surg	NED (30)	Asymptomatic	NA	(43)
Nakazato and Hosaka, 2004	M	32	Brain	4	None	Surg	NA	Epileptic	NA	(44)
Gunlusoy *et al*, 2004	M	59	Adrenal	17	LN	Surg	NA	Lumbar pain	NA	(45)
Sargazi *et al*, 2006	F	45	Adrenal	NA	NA	Surg + RT	AWD (59)	Abdominal pain	NA	(46)
Kurt *et al*, 2007	M	53	Kidney	2	None	Surg	NED (34)	Hematuria	Intermixed	(47)
Nishihara *et al*, 2008	F	32	Brain	3.3	None	Surg + RT	NED (14)	Convulsion	NA	(48)
Neuzillet *et al*, 2008	F	40	Retroperitoneal	NA	Liver	Surg + RT + RFA	AWD (3)	Wilson Mikity syndrome	Intermixed	(49)
Sabatino *et al*, 2009	F	60	Brain	NA	NA	Surg + RT + ChT	NED (18)	Headache	NA	(50)
Riffat *et al*, 2009	M	36	Parotid gland	NA	Local	Surg + ChT	NA	Progressive numbness	NA	(51)
Peycru *et al*, 2009	F	34	Retroperitoneal	8	Local	Surg + RT	NED (3)	Back pain	Nodular	(52)
Mizuno *et al*, 2010	M	53	Adrenal	11	Spine	Surg + RT	AWD (30)	Frequent micturition	Nodular	(6)
Bacher *et al*, 2011	M	37	Bone	NA	Local	Surg + RT + ChT	DOD (48)	Bone pain	Mixed	(53)
Miele *et al*, 2011	M	23	Spinal cord	NA	None	Surg + ChT	NED (12)	Progressive dyspnea	NA	(54)

Table I. Continued.

First author, year	Sex	Age, years	Sites	Size, cm	Metastasis	Initial treatment	Outcome (months)	Symptoms	Histopathology	(Refs.)
Thakar *et al*, 2012	M	30	Spinal cord	NA	None	Surg + ChT	NED (3)	Limb weakness	NA	(55)
Schipper *et al*, 2012	M	28	Brain	5	None	Surg + ChT	NED (14)	Epileptic	NA	(7)
	F	42	Brain	NA	None	Surg (partial) + ChT	AWD (12)	Headache	NA	
Tipps and Weidner, 2012	M	25	Posterior mediastinum	8.3	NA	NA	NA	Polypnea	NA	(56)
Okudera *et al*, 2014	F	53	Filum terminale	3	None	Surg + RT	AWD (228)	Bilateral lower extremity pain	Nodular	(57)
Patnaik *et al*, 2014	M	25	Spinal cord	NA	NA	Surg	NED (4)	Bilateral lower extremity pain, uroschesis	NA	(58)
Akin *et al*, 2014	M	34	Brain	5	NA	Surg + RT	AWD (12)	Headache, bilateral lower extremity numbness	NA	(59)
Jrebi *et al*, 2014	F	22	Adrenal	NA	NA	Surg + ChT + BMT	AWD (156)	Abdominal pain	NA	(60)
	F	26	Spinal cord	NA	NA	Surg + ChT	AWD (108)	Back pain	NA	
	M	33	Retroperitoneal + mediastinum	NA	NA	ChT	DOD (36)	Back pain	NA	
	F	20	Pelvis	NA	NA	Surg + ChT	DOD (60)	Pelvic pain	NA	
Montaut *et al*, 2014	F	19	Adrenal	4	NA	Surg	NA	Hearing impairment	Intermixed	(61)
Chen *et al*, 2014	F	21	Retroperitoneal	17	Local	Surg	NED (5)	Lumbar pain	NA	(62)
Sorrentino	M	23	Abdominal	NA	NA	Surg	DOD (132)	NA	NA	(63)
et al, 2014	M	28	Adrenal	NA	NA	Surg	DOD (130)	NA	NA	
	M	21	Thorax	NA	NA	Surg	NED (154)	NA	NA	
	F	19	Thorax	NA	NA	Surg	NED (100)	NA	NA	
	F	20	Pelvis	NA	NA	Surg + RT	AWD (30)	NA	NA	
Qiu *et al*, 2015	F	27	Adrenal	11	Local	Surg	NED (5)	Lumbar pain	Intermixed	(64)
Ding *et al*, 2015	F	27	Adrenal	11.4	Local	Surg	NA	Lumbar pain	NA	(65)
Bolzacchini *et al*, 2015	M	63	Adrenal	4.5	None	Surg (complete)	NA	Asymptomatic	Nodular	(66)
Moga *et al*, 2016	F	20	Brain	3.2	NA	NA	NA	Neurological symptoms	NA	(67)
Benedini *et al*, 2017	F	20	Adrenal	11	Local	Surg (complete)	NED (21)	Lumbar pain	Intermixed	(68)
Bove *et al*, 2017	M	38	Parotid gland	4	LN	Surg	NED (36)	Asymptomatic	NA	(69)
Risum *et al*, 2017	M	34	Retroperitoneal	8	Postcava, bone	Surg (complete) + RT + ChT	AWD (74)	Abdominal pain	NA	(70)
Lonie *et al*, 2017	M	27	Adrenal	17	None	Surg (complete)	NA	Asymptomatic	Nodular	(71)
Heidari *et al*, 2018	M	38	Adrenal	5.5	None	Surg (complete)	NED (3)	Abdominal discomfort	Nodular	(72)
Kumata *et al*, 2018	F	73	Adrenal	10	None	Surg (complete)	NED (3)	Asymptomatic	Nodular	(73)
Radim *et al*, 2018	M	36	Retroperitoneal	14	NA	Surg (complete)	NED (12)	NA	NA	(74)
Rajendran *et al*, 2019	F	23	Ovarian	7	NA	Surg (complete)	NA	Asymptomatic	NA	(75)

Table I. Continued.

First author, year	Sex	Age, years	Sites	Size, cm	Metastasis	Initial treatment	Outcome (months)	Symptoms	Histopathology	(Refs.)
Mousa *et al*, 2020	F	23	Posterior mediastinum	NA	Bone	Surg (partial) + RT + ChT	AWD (96)	Chest pain	Nodular	(76)
Vassallo *et al*, 2021	M	22	Adrenal	4.2	None	Surg	NED (24)	Abdominal pain, diarrhea	Intermixed	(77)
Filizoglu and Ozguven, 2022	M	39	Posterior mediastinum	NA	Multiple metastases	NA	NA	Chest pain	NA	(78)
Deslarzes *et al*, 2022	F	74	Adrenal	10	None	Surg	NED (1)	Abdominal pain, weakness	Nodular	(4)
Present case	F	20	Adrenal	7.5	Near the renal hilum	Surg (complete)	NED (12)	Asymptomatic	Intermixed	

[a]Due to the considerable age of some reports, they are no longer accessible. Therefore, in a few instances where the original texts were unattainable, other documents have been referenced. AWD, alive with disease; BMT, bone marrow transplantation; ChT, chemotherapy; DOD, died of disease; LN, lymph node; NA, not available; NED, no evidence of disease; RFA, radio-frequency ablation; RT, radiotherapy; Surg, surgery.

Classification in 1999, delineating pNTs into four histopathological types: NB, GNB intermixed type (GNBi), GN mature type and GNB nodular type (GNBn). Based on factors such as patient age, mitosis-karyorrhexis index and cell differentiation, these tumors are further classified into either a favorable histology group or an unfavorable histology group, with implications for prognosis (1,84). The present case was assigned to the favorable histology category according to this classification. Additionally, NB prognosis can be predicted using the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Risk Group (INRG) staging system (85,86). This case was classified as stage 1 in the INSS and stage L1 in the INRG staging, falling into the very low-risk group (risk grouping of A). Consequently, in accordance with pediatric guidelines (1), close follow-up was recommended without the administration of radiotherapy or chemotherapy.

When diagnosing GNB, its clinical presentations are generally non-specific. Among the 104 reported cases, symptoms predominantly arose from compression by the primary or metastatic lesions (8,35,47,60,62,65). Some GNB cases with endocrine activity presented with endocrine-related symptoms such as diarrhea and malaise (4,15,36,49,77). GNBs occurring in the central nervous system more frequently manifested neurological symptoms (7,20,22,23,31,44,48,67). While laboratory tests and imaging studies provide valuable preoperative references, they are not definitive for diagnosis. Pathological examination remains essential for a conclusive diagnosis. In the present case, a mass in the left adrenal gland was identified during a routine physical examination. The CT findings and laboratory tests, including adrenal function, were non-specific. The diagnosis was ultimately established based on the results of a postoperative pathological examination.

The treatment approach for GNB in adults largely mirrors pediatric guidelines, encompassing surgery, radiation therapy and chemotherapy (84). However, specific standardized guidelines or treatment protocols for adults are not established. Previous treatment strategies for adult GNB suggested that adult patients with distant metastases should continue radiotherapy and chemotherapy based on surgical resection (77). However, the present analysis of 24 patients with preoperative metastases and complete follow-up indicated that the choice of treatment in metastatic patients did not influence outcomes significantly (Fig. 6). By contrast, radiotherapy and chemotherapy might adversely impact the quality of life due to more severe side effects. Recent reports (66,68,71-73) have documented complete tumor resection in six cases, with metastases developing in two of them. Follow-up outcomes showed that all six patients achieved disease-free survival. Although the literature suggests that residual tumor does not adversely affect the prognosis in pediatric patients with GNB (87,88), reports in adults imply that complete resection of both primary and metastatic lesions is advisable, irrespective of the presence of metastatic lesions. For patients who cannot undergo a complete resection or who develop postoperative metastases, individualized comprehensive treatment is recommended to optimize survival rates. In the present case, complete surgical resection of the adrenal mass and metastasis was performed. The postoperative pathology and immunohistochemistry classified the case into a histologically favorable prognosis group. Consequently, despite the presence of metastases, and in line with pediatric guidelines and the literature analysis of previous case reports, the patient was advised to undergo close follow-up without further radiotherapy and chemotherapy.

Regarding prognosis and follow-up, the present analysis suggested that abdominal and pelvic lesions, excluding those of the adrenal gland, necessitate thorough preoperative examination and vigilant postoperative monitoring. Despite a lower incidence of metastasis in central nervous system tumors (2/13; 15%), adrenal or intrathoracic tumors may portend a more favorable outcome, often due to their association with more severe clinical symptoms. The interval for recurrence post-surgery varies widely, ranging from 3 months to as long as 192 months (57,59). Notably, a significant number of patients experience recurrence beyond the 2-year postoperative mark. Consequently, we advocate for a rigorous follow-up schedule:

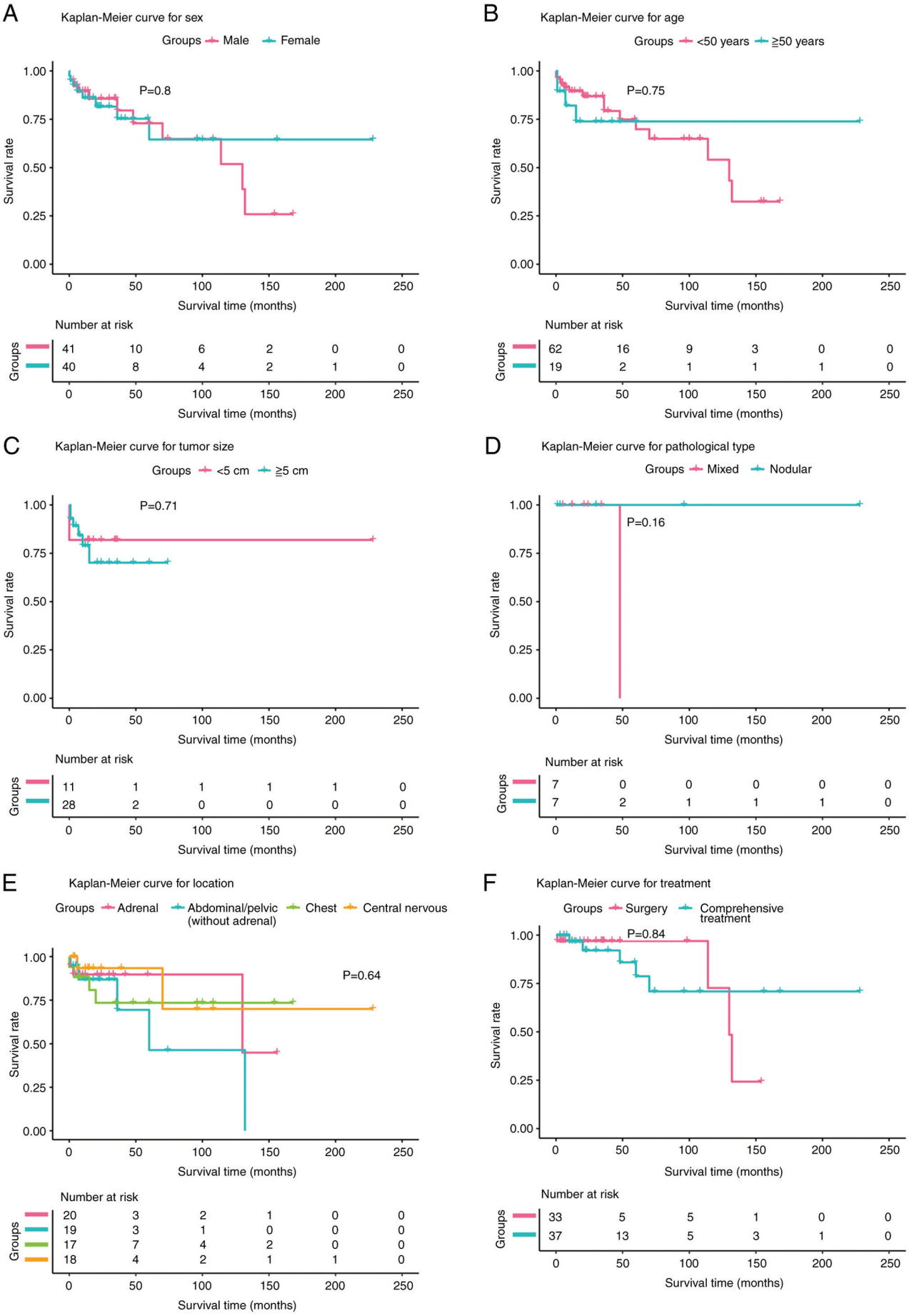

Figure 4. Overall survival curves for patients with different clinical and pathological factors of adult ganglioneuroblastoma. Overall survival curve for (A) sex, (B) age, (C) tumor size, (D) pathological type, (E) location and (F) treatment.

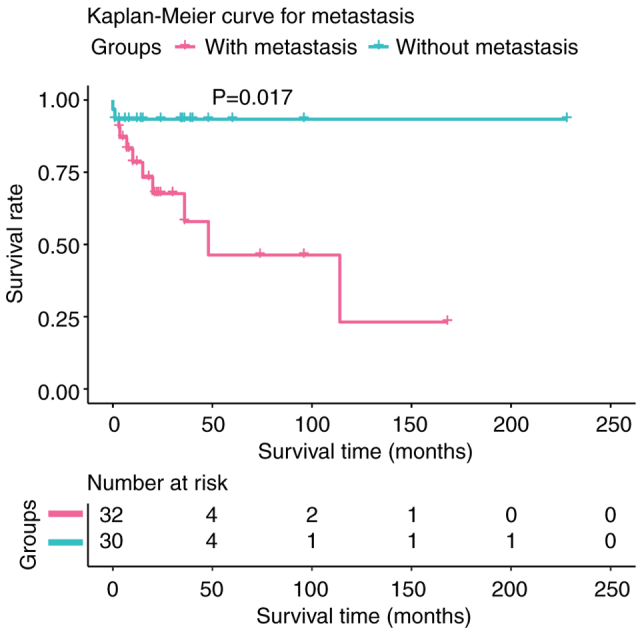

Figure 5. Overall survival curves for patients with or without infiltration or metastasis of adult ganglioneuroblastoma.

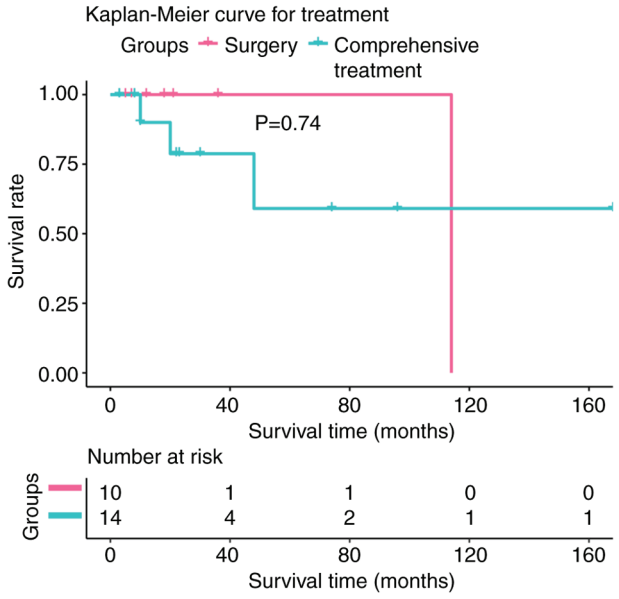

Figure 6. Overall survival curves for patients with infiltration or metastasis with different treatment regimens.

Examinations every 3 months for the first 2 years, followed by biannual check-ups for long-term monitoring.

Although the existing treatment approaches and prognostic assessments for adults with GNB are predominantly derived from pediatric guidelines and associated studies, their effects in managing GNB in adults have shown limitations. There is a pressing need for more comprehensive research specifically focused on adult GNB. The present case report and literature review is vital to enrich our understanding of the disease, increase awareness among physicians and adult patients, alleviate patients' apprehension about the disease, and ultimately, enhance the cure rate.

Table II. Relationship between clinicopathological parameters and metastasis in adult patients with ganglioneuroblastoma.

	Metastasis	
Parameters	Frequencies, n/total n (%)	P-value
Sex		0.891
Male	21/40 (53)	
Female	20/37 (54)	
Age, years		0.117
<50	32/55 (58)	
≥50	8/21 (38)	
Size, cm		0.102
<5	4/14 (29)	
≥5	17/31 (55)	
Pathological type		0.315
Mixed	5/7 (71)	
Nodular	3/9 (33)	
Sites		0.017
Adrenal	11/22 (50)	
Abdominal/pelvic (without adrenal)	12/16 (75)	
Chest	8/16 (50)	
Central nervous	2/13 (15)	

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XZ conceptualized and designed the work, and drafted the study. XS, YZ and XZ participated in data collection and analysis. WL and JW interpreted the data and made significant revisions. JJL and ZZ treated and cared for the patients. DP conducted the analysis of the pathological results. XZ, WL and JL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The First People's Hospital of Yunnan Province (approval no. KHLL2023-KY170).

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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