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소아 복강 내 악성 종양으로 수술 받은 환자에서 발생한 이차 암의 위험 인자 분석

Risk factor analysis for second malignant neoplasm after operation for abdominal malignancies in children

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이 논문을 의학석사 학위논문으로 제출함

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Abstract

Risk factor analysis for second malignant neoplasm after operation for abdominal malignancies in children

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Background: Previous studies have reported on the development of secondary malignant neoplasms (SMNs) after the treatment of primary cancer, but there are scarce studies on the development of SMNs in children who underwent surgery for abdominal malignancies.

Methods: This was a retrospective study comprised of 342 patients who were diagnosed and underwent surgery for abdominal malignant tumors between January 2005 and December 2017 at Seoul National University Children's Hospital. We explored the risk factors for the development of SMN. Basic patient characteristics, such as age, sex, diagnosis, operation-related factors, and factors associated with the treatment, including the dose of anticancer drugs, radiotherapy (RT), and stem cell transplantation (SCT), were investigated. Statistical analyses were performed through group comparison using t-tests or chi-squared tests, when appropriate, and Cox logistic regression analysis. P-values of < 0.05 were considered statistically significant.

Results: Among 342 patients, nine patients experienced SMNs. The median age at surgery for primary cancer was 3.9 years and the number of males was 193 (56.4%). The most common primary cancer diagnosis neuroblastoma, at 110 (32.1%). The types of SMNs included

renal cell carcinoma and acute myeloid leukemia after treatment of the neuroblastoma. When comparing the group with SMNs and the group without, the significant factors were reoperation, the number of operations, RT, chemotherapy, SCT, and some anticancer drugs, such as cisplatin, etoposide, and cyclophosphamide. In multivariate analysis, reoperation and SCT were significant factors for developing SMNs. The overall 5-year survival rate was 80.3% in all patients. When comparing the survival by SMN occurrence, the 5-year overall survival rate was not different significantly (87.5% in SMNs, and 80.1% in non-SMNs, $p = 0.487$).

Conclusion: The results suggest that reoperation and SCT were associated with developing SMNs in children who underwent surgery for abdominal cancer. Close surveillance for assessing long-term risks and guidance for appropriate long-term follow-up is required for children with abdominal malignancies who received reoperations or SCT.

Keywords: Abdominal neoplasms, Pediatrics, Second primary neoplasms, Radiotherapy, Chemotherapy, Stem cell transplantation

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INTRODUCTION

With the introduction of various treatment methods, including surgery, chemotherapy, radiation therapy (RT), and stem cell transplantation (SCT), the survival rate of childhood cancer has increased over time. Concomitant with the increasing survival rate, interest in the various medical problems these cancer survivors will face is increasing.(1) Secondary primary tumors are a different type of malignant tumor than the primary cancer that occur after the primary cancer. Various terms are used to refer to it, such as secondary malignant neoplasm (SMN), subsequent malignant neoplasm, and secondary cancer.(2-4) It is one of the worst outcomes for cancer survivors.

Several studies have reported the incidence rate of SMN after childhood cancer. A study conducted in Japan reported an incidence of 2.6% for SMN with a 20-year follow-up after diagnosis,(3) whereas a study conducted in the Netherlands reported a 3.9% incidence with a 25-year follow-up.(5) According to a study reported in South Korea using the Korean Central Cancer Registry, SMNs had occurred in 2% of patients with a diagnosis of childhood cancer by a 15-year follow-up.(4) Poorer survival was reported for patients with SMNs than for patients without them.(4)

To date, studies on the occurrence of SMN have been conducted in all pediatric cancer patients,(2, 3, 6, 7) patients with a specific diagnosis,8-10 those who received certain kinds of treatment,(11-14) and those who received certain treatments from certain diseases.(15-17) Based on these studies, many factors involved in the occurrence of a SMN were identified, including the primary diagnosis, RT, SCT, and certain genes expressed in the tumor.(2, 3, 6, 7, 10-13)

However, few studies have been conducted in patients who underwent surgery for pediatric abdominal cancer. This study was conducted on patients who had follow-ups in a single center. Distinct from a population-based study, the exact doses of anticancer drugs and RT were reviewed in detail to assess the risk for SMNs.

METHODS

Patients

This retrospective single-center study was conducted at Seoul National University Children's Hospital. We reviewed the data of pediatric patients who underwent surgery for abdominal malignant tumors between January 2005 and December 2017. The electronic schedule of pediatric surgery was reviewed for the study period. We screened and selected potential surgeries for inclusion in the study by operation name and diagnosis in the schedule. Surgeries that did not have a start and end time reported were reviewed in the anesthesia and surgical records. Operations without these records were excluded. The pathological results of the 1,061 surgeries initially screened were reviewed. Operations for congenital malformations, inflammatory disease, hematomas, and those with no pathological results were excluded (Fig. 1). The patient characteristics of tumor location; tumor size; method of operation; the intent of the operation; the total number of surgeries; pathologic results; secondary tumors; adjuvant therapy, including chemotherapy, RT, and SCT; as well as follow-up data were investigated. The doses of chemotherapeutic agents administered to the patients were collected by reviewing the chemotherapy reports for each patient. All doses were converted to dose per body surface area (m^2) using body weight and height in the Mosteller formula.(18)

Ethical statement

This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB number: 1811-053-983). The requirement to obtain informed consent was waived by the IRB because of the retrospective nature of this study. All methods used in this study were

performed in accordance with the relevant guidelines and regulations.

Definition

Malignant or benign disease was determined based on the pathology results. Tumor size was defined as the longest diameter in the pathology reports and radiologic examinations were used in cases of fragmented tumors. The number of operations was counted only for the same lesion. Operations for distinct lesions in the same patient were counted separately. Operations before the study period were counted in the number of surgeries but excluded from further analyses. Secondary tumors were investigated only for patients with malignancies, which included benign and malignant tumors distinct from the primary malignancy arising at any site. Tumor location was categorized by considering the location and origin in the adrenal gland, coccyx, colon, gallbladder, liver, mesentery, omentum, ovary, pancreas, pelvis, peritoneum, presacral area, rectum, retroperitoneum, small bowel, spleen, stomach, and other sites. The intent of the operation was categorized as either an incisional biopsy or an excision. Classification as an incisional biopsy was assigned only for the initial diagnosis of the primary tumor. Operations for suspected recurrence were considered excisions. The total doses of each chemotherapeutic agent were summed by reviewing the administration history of all drugs. The date of death and the reason for death were obtained from the Korea National Statistical Office through our institution with study consent approved by the IRB. We were able to determine the date of death for patients lost to follow-up who died before December 31, 2017, but not for those who died later. The patients with primary neuroblastoma were divided according to risk group to compare the incidence of second neoplasms. The low-risk group was defined as patients who underwent only surgery. The intermediate group was defined as patients who

underwent surgery and chemotherapy without RT nor SCT. The high-risk group was defined as patients who underwent surgery, chemotherapy, and RT or SCT.

Statistical Analysis

All continuous variables are presented as median values and interquartile ranges. The Mann-Whitney U test and student's t-test were used to compare continuous data, when appropriate, whereas the Chi-squared test was used to analyze categorical data. Cumulative hazard curves were obtained with a Kaplan-Meier estimator. A log-rank test was performed to compare the curves. Multivariable logistic regression was used to determine the association between the factors and SMN occurrence. Variables with $P < 0.05$ were entered as the input variables in a multivariate model. SPSS version 23 (IBM Corporation, Armonk, NY, USA) was used for the Cox proportional hazards model analysis. Descriptive statistics and survival curves were obtained using R statistical software (version 3.2.3 R Foundation for Statistical Computing, Vienna, Austria). A P-value < 0.05 was considered statistically significant.

RESULTS

Demographics of all patients

The detailed demographics of all patients is available in Table 1. Of the total 342 patients, 193 were males (56.4%) and 149 were females (43.6%). The median age was 3.9 years old (IQR [interquartile range]: 1.6 – 10.0). Among the primary cancers, neuroblastoma was the most common (111; 32.4%), followed by germ cell tumors (GCT) (64; 18.7%), hepatoblastomas (50; 14.6%), solid pseudopapillary tumors (SPT) (20; 5.8%), and hematolymphoid malignancies (HLM) (20; 5.8%). The cancer was located in the adrenal glands in 90 patients (26.2%), the coccyx in 13 patients (3.8%), the colon in three patients (0.9%), the liver in 59 patients (17.2%), the mesentery in six patients (1.7%), the ovaries in 24 patients (7.0%), the pancreas in 21 patients (6.1%), the pelvis in nine patients (2.6%), the pre-sacrum region in six patients (1.7%), the retroperitoneum region in 86 patients (25.1%), the small bowel in 12 patients (3.5%), and other areas in 13 patients (3.8%). The median size of the cancers was 5.4 cm (IQR: 3.5–8.8). Primary excisions were performed in 291 patients (85.1%) and primary biopsies in 51 patients (14.9%). Open surgery was performed in 260 patients (76.2%), laparoscopic surgery in 67 patients (19.6%), and conversion surgery in 14 patients (4.1%). SMNs occurred in nine patients (2.6%). Ninety-six patients (28.1%) underwent reoperations. Chemotherapy was performed in 242 patients (70.8%), RT in 77 patients (22.5%), and SCT in 70 patients (20.5%).

Cases of second malignancies

Table 2 lists all cases of SMNs. The SMNs included renal cell carcinoma after neuroblastoma, myelodysplastic after neuroblastoma, squamous cell carcinoma in the nose after neuroblastoma, acute myeloid leukemia after

neuroblastoma, myelodysplastic syndrome (MDS) after germ cell tumor, mucoepidermoid carcinoma in the salivary gland after germ cell tumor, acute myeloid leukemia after nephroblastoma, renal cell carcinoma (RCC) after solid pseudopapillary neoplasm, and inflammatory myofibroblastic tumor after mucinous cystadenocarcinoma in the ovary. Four patients were treated with reoperations, RT, chemotherapy, and SCT. Three patients received three of these treatments and one patient each received two and one of these treatments.

Comparison of patients with second malignant neoplasms and second benign neoplasms

There were 20 cases of second neoplasms, nine of which were malignant and 11 of which were benign (Table 3). Various factors were analyzed, including sex, age, location, size of cancer, surgical method, surgical procedure, anticancer drugs, RT, and SCT. However, no significant factors were found.

Comparisons of second malignancies and non-second malignancies

Age, tumor location, tumor size, primary operation type and method, the reason for the reoperation, resection margin, and mortality did not show significant differences. Reoperations and the number of operations were significantly different. Reoperation was more common in the SMN group (26.7% vs. 77.8%, p = 0.002) (Table 4). Comparison of the types of chemotherapy and their doses is given in Table 5. Comparison of RT and SCT is shown in Table 6. Among the many types of anticancer drugs, the significant variables between the second malignancy group and non-second malignancy groups were etoposide (median: 2650.0 vs 460.0, p = 0.028), cyclophosphamide (median: 12600.0 vs 0.0, p = 0.029), thiotepa (median: 0.0 vs 0.0, p = 0.044), carboplatin (median: 3600.0 vs 0.0, p =

0.021), melphalan (median: 0.0 vs 0.0, p = 0.006), and ifosfamide (median: 6000.0 vs 0.0, p = 0.026). Comparison between the second malignancy and those in the non-groups revealed significant differences in RT (p = 0.001), RT dose (p < 0.001), and SCT (p < 0.001). The median RT dose was 0.0 Gy and the IQR was 0.0 to 0.0 in the group without SMNs, whereas the median was 15.0 Gy and the IQR was 12.0 to 30.0 in the group with SMNs. In multivariate analysis with variables that were significant in univariate comparison analysis, reoperation (p = 0.027) and SCT (p = 0.026) were significant (Table 7).

Cumulative incidence according to factors

A graph of the cumulative incidence of SMNs in the entire patient population is shown in Figure 2. The 5-year and 10-year incidences of SMNs were 1.2% (95% confidence interval: 0 – 2.6%) and 7.3% (1.8 – 12.8%), respectively. Figure 3 shows the incidence of SMNs according to reoperation, chemotherapy, RT, and SCT. The 5-year and 10-year rates were 0% and 3.4% in the group without reoperation, 4.5% and 20.3% in the group without reoperation, 0% and 3.8% in the group without chemotherapy, and 1.7% and 9.1% in the group treated with chemotherapy, respectively. The non-RT group was 0.4% and 0.4% and the group with RT was 3.8% and 23.2%, respectively. The rates were 0% and 1.8% in the group without SCT and 6.2% and 29.6% in the group with SCT, respectively. Significant differences were reoperation (p < 0.001), RT (p = 0.001), and SCT (p < 0.001).

Comparison of survival between second malignancies and non-second malignancies

Figure 4 shows the survival rate according to whether an SMN occurred. The 5-year overall survival rate was 80.1% and the 10-year overall

survival rate was 77.9% in the group without SMNs. The 5-year overall survival rate was 87.5% and the 10-year survival was 50.0% in the group of patients with SMNs. However, no statistical difference was found ($p = 0.487$). When a survival curve was drawn according to second benign tumors and SMNs, a difference in the survival rate was found. In benign tumors, the 5-year survival rate was 100% and the 10-year survival rate was 100%, whereas, in malignant tumors, they were 87.5% and 50.0%, respectively ($p = 0.041$) (Fig. 5).

Cumulative incidence according to the neuroblastoma risk group

The number of patients in the low, intermediate, and high-risk groups was 31, 23, and 57, respectively. The number of second neoplasms in patients with primary neuroblastomas was 13. Second neoplasms occurred solely in the high-risk group. The cumulative incidence of second neoplasms was statistically different according to the neuroblastoma risk group ($p < 0.001$, Fig. 6). Among 13 cases of second neoplasms, four cases were malignant. The cumulative incidence was not statistically different when limited to second malignant neoplasms ($p = 0.119$, Fig. 7).

DISCUSSION

This study investigated the incidence and associated risk factors for SMNs after treatment for abdominal cancer in pediatric patients. Of the 342 patients, 110 of the primary cancers were neuroblastomas, nearly one-third. More than one operation was performed in 96 patients (28.1%). Chemotherapy, RT, and SCT were performed in 70.8%, 22.5%, and 20.5% of the patients, respectively. In univariate analysis, the factors affecting the development of SMN were reoperation, some anticancer drugs, RT, and SCT. Chemotherapy itself was not a significant factor. The study found that radiation therapy was a significant risk factor for the development of SMN, but chemotherapy was not, which was consistent with the findings at eight hospitals in France and the UK.(19) Multivariate logistic analysis with these significant variables showed that reoperation and SCT were significant factors, whereas chemotherapy and RT were not. The survival was not significantly different between the SMN group and the non-SMN group.

Although multidisciplinary therapy has improved the therapeutic outcomes of children with cancer, the treatments themselves also increase the risk of subsequent late effects.(20) According to Kleinerman et al., RT was the most aggravating factor that increased the risk of SMN by 3-fold in patients with hereditary retinoblastomas.(21) An increased risk of SMN was observed in a study cohort of 1,487 pediatric autologous SCT recipients.(11) In our study, the cumulative 10-year incidence rate was about 7.5%. These rates were higher than the previously reported rates in a large POGNOSIS registry study by Pole et al., showing a 15-year incidence of 2.5% in the autologous SCT group and 2.3% in the non-SCT group.(14) The results in the Korean Central Cancer Registry of patients diagnosed with childhood cancer between 1993 and 2012 showed SMNs in

337 of the total 28,405 patients (1.2%) at 10 years.(4) Compared to this result, the SMN rate in this study was a little higher. Cohort differences, such as diagnosis, race, and the course of treatment, in the other studies may have contributed to the difference in the incidence of SMN.

Among the cases of SMNs, one patient developed RCC after treatment for neuroblastoma. The patient received surgery, RT, chemotherapy, and SCT treatments. According to Federico et al., one female patient with neuroblastoma in the adrenal gland at 3.1 years of age developed RCC in the left kidney at 27.3 years old after a 24.2 year latency period. The anticancer drugs she received for treatment of the first cancer included cyclophosphamide, doxorubicin, cisplatin, and teniposide, but no RT.(9) In this study, the median latency from the diagnosis of neuroblastoma to the diagnosis of carcinoma, including RCC was 24.2 years (range, 5.8 to 44.2 y), whereas the median latency from the diagnosis of neuroblastoma to the diagnosis of all types of SMNs (n = 9) was 10.7 years (range, 1.3 to 44.2 y). One female patient in our study had neuroblastoma in the retroperitoneum and after surgery, RT, chemotherapy, and SCT, she developed acute myelogenous leukemia (AML). According to Federicoet al., one female patient with neuroblastoma in the adrenal gland at 8.7 years of age developed acute myelomonocytic leukemia at 10.0 years old after a 1.3 year latency period.(9) The anticancer drugs she received to treat the first cancer included cyclophosphamide, doxorubicin, cisplatin, and teniposide, but no RT. The median latency from the diagnosis of neuroblastoma to the diagnosis of AML/MDS (n = 4) was 3.6 years (range, 1.3 to 5.4 y). According to a review article, the most common SMNs are RCCs, AML, and thyroid cancer.(22) Also, in previously published results from the Childhood Cancer Survivor Study (CCSS), 30 neuroblastoma survivors developed an SMN (standardized incidence rate (SIR) = 8.0; 95%

CI = 5.4 – 11.4) five or more years following the first diagnosis.(23) The study results showed that the SMNs that occurred five or more years after the original cancer diagnosis were thyroid cancer (SIR = 23.6, 95% CI = 10.2 – 46.5), RCC (SIR = 89.4, 95% CI = 28.8 – 208.7), soft tissue sarcomas (SIR = 20.6, 95% CI = 4.1 – 60.1), AML (SIR = 186.9, 95% CI = 21.0 –674.9), breast cancer (SIR [among female survivors] = 12.8, 95% CI = 1.4 – 46.2), brain tumors (SIR = 5.2, 95% CI = 0.6 – 18.9), acute lymphoblastic leukemia (n = 1), Hodgkin lymphoma (n = 1), and others (n = 7). This data also showed that RCC and AML represented a high proportion of the SMNs. In our study, in four of the nine cases of SMN, the primary cancer was neuroblastoma. Some studies reported that the risk of developing bone sarcoma after neuroblastoma was high.(24, 25) In our study, no new sarcomas were observed. Mucoepidermoid carcinoma in the salivary glands and MDS developed in two patients with germ cell tumors. A German study of SMNs in germ cell tumors found that the risk of developing malignant tumors increased by seven times in patients treated with RT compared to the male German population.(26) Note that this study aimed to analyze the results of an SMN in a patient treated with testicular cancer, so all the patients are male. In our study, two malignant tumors and one benign tumor occurred in germ cell tumors, all three of which occurred in females. According to a U.S. and Canadian retrospective study that assessed the risk of SMNs using the CCSS cohort, the risk of developing SMN was increased by RT.(27) In our study, carcinoma developed in four out of nine SMN patients, all of whom received RT.

Autologous SCT is one of the treatment modalities for hematologic and solid tumors in pediatric patients and high-dose chemotherapy with or

without RT is used as a conditioning regimen for autologous SCT to achieve tumor death and consolidate therapy. There are concerns about the strong nature of these anticancer drugs, which can cause the development of an SMN. In our study, the doses of chemotherapy were reviewed in detail, but none were significantly associated with SMNs in multivariate analysis. However, in the CCSS cohort study, etoposide was found to be significant among the anticancer drugs. In multivariable Poisson regression analysis, exposure to any RT ($p = 0.05$) and etoposide ($p = 0.01$) were statistically significant risk factors for the development of SMN.(23)

RT has been studied as an important factor in the development of SMN in many studies. In a multi-center retrospective study in Korea, a patient who was first diagnosed with neuroblastoma and irradiated with 1500 cGy of radiation to the kidney had a subsequent RCC after a 7.5-year latency period.(7) According to Harbron et al., RT-treated childhood cancer patients were nearly five times more likely to develop neoplasms later than the general population under 29 years of age.(13) In addition, in a German nested case-control study, RT in the neck or spine increased the risk of thyroid cancer and exposure to the neck also increased the risk of other solid malignancies to a similar degree.(28) However, in our study, RT was significant in the univariate analysis but not in the multivariate analysis.

The results of our study indicate that survivors of childhood cancer treated with SCT had a nearly 7.4-fold greater risk of developing a further malignant neoplasm compared to the population without SCT. According to Pole et al., patients who received autologous SCTs had a 3.3 times higher history of relapse.(14) However, one study found no difference in the cumulative incidence of SMN, depending on whether or

not SCT was performed.(3) Further studies are needed to confirm the effect of SCT on the development of SMN in children. Reoperation was found to be a risk factor for developing SMN in our study, but studies analyzing the association between reoperation and SMN are scarce. Therefore, further studies on reoperation as a risk factor for SMN are required.

By reviewing the detailed anticancer dosage records, which is difficult to do in a population-based study, we were been able to investigate the effects of anticancer drugs on SMN. However, a limitation of this study was that the number of samples was small because it did not target information collected from other medical centers. Also, the data in this study was collected from 342 people in a single tertiary care institution for about 13 years from 2005 to 2017. Thus, it was not a long-term study. In addition, because some patients dropped out during the observation period, the number of patients with an SMN could have been greater. Because of the low numbers of patients, subgroup analysis, such as the effect of primary tumors on SMN development, was not possible. The fact that radiation treatment was not significant was also due to the low power resulting from the small number of patients analyzed.

The results of our study showed that children who underwent SCT and reoperation were at risk for developing SMNs after primary abdominal malignancies. Continuous management and check-ups for SMNs will be important in these patients. Future work should be undertaken to minimize the incidence of SMN after the treatment of abdominal malignancies in children.

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Table1. Demographics of patients who underwent surgery for malignant abdominal tumors

	Malignant abdominal tumor (N=342)
Sex	
Male	193 (56.4%)
Female	149 (43.6%)
Age (y, median, IQR)	3.9 (1.6-10.0)
Diagnosis	
Neuroblastoma	111 (32.4%)
GCT	64 (18.7%)
Hepatoblastoma	50 (14.6%)
SPT	20 (5.8%)
HLM	20 (5.8%)
Rhabdomyosarcoma	15 (4.3%)
Others	62 (18.1%)
Location	
Adrenal	90 (26.2%)
Coccyx	13 (3.8%)
Colon	3 (0.9%)
Liver	59 (17.2%)
Mesentery	6 (1.7%)
Ovary	24 (7.0%)
Pancreas	21 (6.1%)
Pelvis	9 (2.6%)
Pre-sacrum	6 (1.7%)
Retroperitoneum	86 (25.1%)
Small bowel	12 (3.5%)
Others	13 (3.8%)
Size (cm, median, IQR)	5.4 (3.5-8.8)
Operation type	
Excision	291 (85.1%)
Incisional biopsy	51 (14.9%)
Operation method	
Open*	274 (80.4%)
Laparoscopy	67 (19.6%)
Number of operations	
1	246 (71.9%)
2	65 (19.0%)
3 or more	31 (9.1%)
Reason for reoperation	
Suspected recurrence	15 (4.4%)
Recur/residu/meta	81 (23.7%)
Resection margin	
0	216 (63.2%)
1	43 (12.6%)
2	82 (24.0%)
Chemotherapy	242 (70.8%)
Radiotherapy	77 (22.5%)
Stem cell transplantation	70 (20.5%)
Second neoplasm	20 (5.8%)
Benign	11 (3.2%)
Malignant	9 (2.6%)

y: year, IQR: interquartile range, GCT: germ cell tumor, SPT: solid pseudopapillary tumor, HLM: hematolymphoid malignancy

*14 patients were open conversions from laparoscopies

Table2. Details of patients with second neoplasm

	Sex	Primary diagnosis	Location	Reop	RT	CTx	SCT	Second Neoplasm
Malignant Neoplasm								
1	M	Neuroblastoma	Adrenal gland	Yes	Yes	Yes	Yes	Renal cell carcinoma
2	M	Neuroblastoma	Adrenal gland	Yes	Yes	Yes	Yes	Myelodysplastic syndrome
3	M	Neuroblastoma	Adrenal gland	No	Yes	Yes	Yes	Squamous cell carcinoma, nose
4	F	Neuroblastoma	Retroperitoneum	Yes	Yes	Yes	Yes	Acute myeloid leukemia, M4
5	F	Germ cell tumor	Retroperitoneum	Yes	No	Yes	Yes	Myelodysplastic syndrome
6	F	Germ cell tumor	Coccyx	No	Yes	No	Yes	Mucoepidormiod carcinoma, salivary gland
7	F	Wilms tumor	Retroperitoneum	Yes	Yes	Yes	Yes	Acute myeloid leukemia, M5
8	F	Solid pseudopapillary neoplasm	Pancreas	Yes	Yes	Yes	No	Renal cell carcinoma
9	F	Ovary mucinous cystadenocarcinoma	Ovary	Yes	No	No	No	Inflammatory myofibroblastic tumor, liver
Benign Neoplasm								
1	M	Neuroblastoma	Adrenal gland	Yes	Yes	Yes	No	Focal nodular hyperplasia, liver
2	M	Neuroblastoma	Adrenal gland	Yes	Yes	Yes	No	Focal nodular hyperplasia, liver
3	F	Neuroblastoma	Adrenal gland	No	Yes	Yes	Yes	Focal nodular hyperplasia, liver
4	F	Neuroblastoma	Adrenal gland	No	Yes	Yes	Yes	Focal nodular hyperplasia, liver
5	F	Neuroblastoma	Retroperitoneum	Yes	Yes	Yes	No	Focal nodular hyperplasia, liver
6	F	Neuroblastoma	Retroperitoneum	No	Yes	Yes	Yes	Focal nodular hyperplasia, liver
7	M	Neuroblastoma	Adrenal gland	No	Yes	Yes	Yes	Myofibroma, bladder
8	M	Neuroblastoma	Adrenal gland	No	Yes	Yes	Yes	Osteochondroma, femur, Rt.
9	M	Neuroblastoma	Retroperitoneum	Yes	No	Yes	Yes	Hepatocellular adenoma
10	F	Germ cell tumor	Small bowel	Yes	No	Yes	No	Parosteal osteochondroma
11	F	Rhabdomyosarcoma, Embryonal	Liver	Yes	Yes	Yes	No	Focal nodular hyperplasia Uterine myoma,

Reop: Reoperation, RT: Radiotherapy, CTx: Chemotherapy, SCT: Stem cell transplantation

Table 3. Comparison of patients with second malignant neoplasms and second benign neoplasms

	Second Malignant Neoplasm (N=9)	Second Benign Neoplasm (N=11)	P-value
Female	6 (66.6%)	6 (54.5%)	0.582
Age (Median, year, IQR)	6.0 (3.3–12.0)	3.9 (1.8-7.0)	0.322
Location			0.573
Adrenal gland	3 (33.3%)	6 (54.5%)	
Coccyx	1 (11.1%)	0 (0%)	
Liver	1 (11.1%)	1 (9.1%)	
Pancreas	1 (11.1%)	0 (0%)	
Retroperitoneum	3 (33.3%)	3 (27.3%)	
Small bowel	0 (0%)	1 (9.1%)	
Tumor size (cm, median, IQR)	5.0 (4.2 – 6.7)	7.0 (2.8 - 8.5)	0.909
Diagnosis			0.295
Neuroblastoma	4 (44.4%)	9 (81.8%)	
GCT	2 (22.2%)	0 (0%)	
SPT	1 (11.1%)	0 (0%)	
Rhabdomyosarcoma	0 (0%)	1 (9.1%)	
Others	2 (22.2%)	1 (9.1%)	
Operation type			0.099
Excision	7 (77.8%)	11 (100%)	
Incisional biopsy	2 (22.2%)	0 (0%)	
Method			0.353
Open	9 (100%)	10 (90.9%)	
Laparoscopy	0 (0%)	1 (9.1%)	
Reoperation	7 (77.8%)	6 (54.5%)	0.279
Reason for reoperation			0.559
Suspected recur	1 (14.3%)	2 (33.3%)	
Recur/residu/meta	6 (85.7%)	4 (66.7%)	
Resection margin			0.072
0	5 (55.6%)	2 (18.2%)	
1	0 (0.0%)	4 (36.4%)	
2	4 (44.4%)	5 (45.5%)	
Chemotherapy*			
Cisplatin	300.0 (265.0-487.0)	320.0 (0.0-420.0)	0.789
Etoposide	2596.0 (2337.0-4400.0)	2650.0 (1500.0-3800.0)	0.621
Cyclophosphamide	13300.0 (9915.0-34599.0)	12600.0 (0.0-15510.0)	0.267
Adriamycin	150.0 (130.5-390.0)	150.0 (0.0-210.0)	0.194
Topotecan	10.0 (5.0-52.0)	0.0 (0.0-10.0)	0.100
Thiotepa	900.0 (342.0-900.0)	0.0 (0.0-900.0)	0.102
Carboplatin	2900.0 (2900.0-3720.0)	3600.0 (0.0-3810.0)	0.759
Melphalan	0.0 (0.0-210.0)	210.0 (0.0-210.0)	0.425
Ifosfamide	6000.0 (0.0-27000.0)	0.0 (0.0-12700.0)	0.368
Radiotherapy	7 (77.8%)	9 (81.8%)	0.822
Stem cell transplantation	7 (77.8%)	6 (54.5%)	0.279
Interval SN (median, mon, IQR)	111.2 (61.5-156.0)	100.2 (35.2-116.7)	0.287

*All chemotherapeutic agents are presented as mg/m^2, median, and interquartile range
IQR: interquartile range, GCT: germ cell tumor, SPT: solid pseudopapillary tumor, Interval SN: period between the 1st surgery and 2nd neoplasm, mon: month

Table 4. Comparison of demographics according to the occurrence of second malignancies

	SM (-) (N=333)	SM (+) (N=9)	P-value
Female	146 (43.8%)	3 (33.3%)	0.737
Age (y, median, IQR)	3.9 (1.6-10.0)	3.9 (1.8-7.0)	0.854
Diagnosis			0.772
Neuroblastoma	107 (32.1%)	4 (44.4%)	
GCT	62 (18.6%)	2 (22.2%)	
Hepatoblastoma	50 (15%)	0 (0%)	
SPT	19 (5.7%)	1 (11.1%)	
HLM	20 (6.0%)	0 (0%)	
Rhabdomyosarcoma	15 (4.5%)	0 (0%)	
Others	60 (18.0%)	2 (22.2%)	
Tumor location			0.498
Adrenal gland	86 (25.8%)	3 (33.3%)	
Coccyx	12 (3.6%)	1 (11.1%)	
Liver	58 (17.4%)	1 (11.1%)	
Ovary	24 (7.2%)	0 (0.0%)	
Pancreas	20 (6.0%)	1 (11.1%)	
Retroperitoneum	83 (24.9%)	3 (33.3%)	
Others	50 (15.0%)	0 (0.0%)	
Tumor size (cm, median, IQR)	5.1 (3.3-8.5)	7.0 (2.8-8.5)	0.933
Operation type			0.628
Excision	284 (85.3%)	7 (77.8%)	
Incisional biopsy	49 (14.7%)	2 (22.2%)	
Operation method			0.133
Open	266 (79.9%)	9 (100.0%)	
Laparoscopy	67 (20.1%)	0 (0.0%)	
Reoperation	89 (26.7%)	7 (77.8%)	0.002
Reason for reoperation			>0.99
Suspected recur	14 (15.7%)	1 (14.3%)	
Recur/residu/meta	75 (84.3%)	6 (85.7%)	
Resection margin			0.240
0	211 (63.6%)	5 (55.6%)	
1	43 (13.0%)	0 (0.0%)	
2	78 (23.5%)	4 (44.4%)	
Number of operations			0.002
1	244 (73.3%)	2 (22.2%)	
2	61 (18.3%)	4 (44.4%)	
3 or more	28 (8.4%)	3 (33.3%)	
Mortality	61 (18.3%)	3 (33.3%)	0.378
Follow-up period (mon, median, IQR)	58.0 (20.2-98.5)	106.5 (66.5-117.8)	0.093

SM: second malignancy, y: year, IQR: interquartile range, GCT: germ cell tumor, SPT: solid pseudopapillary tumor, HLM: hematolymphoid malignancy

Table 5. Comparison of chemotherapy dose according to occurrence of second malignancy

	SM (-) (N=333)	SM (+) (N=9)	P-value
Chemotherapy	235 (70.6%)	7 (77.8%)	>0.99
Cisplatin (mg/m^2, median, IQR)	108.0 (0.0-374.0)	320.0 (0.0-420.0)	0.385
Etoposide (mg/m^2, median, IQR)	460.0 (0.0-2270.0)	2650.0 (1500.0-3800.0)	0.028
Bleomycin (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.812
Irinotecan (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.349
Fluorouracil (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.286
Leucovorin (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.643
Bevacizumab (mg/m^2, median, range)	0.0 (0.0–580.0)	0.0 (0.0-0.0)	1.000
Cyclophosphamide (mg/m^2, median, IQR)	0.0 (0.0-6500.0)	12600.0 (0.0-15510.0)	0.029
Adriamycin (mg/m^2, median, IQR)	0.0 (0.0-163.0)	150.0 (0.0-210.0)	0.592
Topotecan (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-10.0)	0.209
Thiotepa (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-900.0)	0.044
Carboplatin (mg/m^2, median, IQR)	0.0 (0.0-1905.0)	3600.0 (0.0-3810.0)	0.021
Melphalan (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-210.0)	0.006
Vincristine (mg/m^2, median, IQR)	0.0 (0.0-1.5)	0.0 (0.0-0.0)	0.076
Ifosfamide (mg/m^2, median, IQR)	0.0 (0.0-0.0)	6000.0 (0.0-27000.0)	0.026
Busulfan (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.566
Doxorubicin (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.602
Dactinomycin(mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.491
Atropine (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.602
Temozolomide.p.o. (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.519
Daunomycin (mg/m^2, median, range)	0.0 (0.0–172.0)	0.0 (0.0-0.0)	1.000
6-Merkaptopurin (mg/m^2, median, range)	0.0 (0.0–11210.0)	0.0 (0.0-0.0)	1.000
Imatinib (mg/m^2, median, range)	0.0 (0.0–9520.0)	0.0 (0.0-0.0)	1.000
Fludarabine (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.691
Epirubicine (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.643
Vinblastine (mg/m^2, median, IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.464

	SM (-) (N=333)	SM (+) (N=9)	P-value
Paclitaxel (mg/m^2, median, range)	0.0 (0.0-1250.0)	0.0 (0.0-0.0)	1.000
Gemcitabine (mg/m^2, median, range)	0.0 (0.0–9000.0)	0.0 (0.0-0.0)	1.000
Oxaliplatin (mg/m^2, median, range)	0.0 (0.0–935.0)	0.0 (0.0-0.0)	1.000
Thioguanine (mg/m^2, median, range)	0.0 (0.0–21150.0)	0.0 (0.0-0.0)	1.000
Docetaxel (mg/m^2, median, range)	0.0 (0.0–740..0)	0.0 (0.0-0.0)	1.000
Rituximab (mg/m^2, median, range)	0.0 (0.0–1500.0)	0.0 (0.0-0.0)	1.000
Behenoyl (mg/m^2, median, range)	0.0 (0.0-5790.0)	0.0 (0.0-0.0)	1.000
Idarubicin (mg/m^2, median, range)	0.0 (0.0-104.0)	0.0 (0.0-0.0)	1.000
Mitoxantrone (mg/m^2, median, range)	0.0 (0.0–52.0)	0.0 (0.0-0.0)	1.000
Carmustine (mg/m^2, median, range)	0.0 (0.0–672.0)	0.0 (0.0-0.0)	1.000
Vinorelbine (mg/m^2, median, range)	0.0 (0.0–225.0)	0.0 (0.0-0.0)	1.000
Dacarbazine (mg/m^2, median, range)	0.0 (0.0–225.0)	0.0 (0.0-0.0)	1.000
Methotrexate (mg/m^2, median, range)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.477
Cytarabine (mg/m^2, median, range)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.477
Regimen number (EA, median, IQR)	1 (0-2)	2 (2-2)	0.278

SM: second malignancy

Table 6. Comparison of radiotherapy and stem cell transplantation according to occurrence of second malignancy

	SM (-) (N=333)	**SM (+) (N=9)**	**P-value**
Radiotherapy	70 (21.0%)	7 (77.8%)	0.001
dose (Gy, median, IQR)	0.0 (0.0-0.0)	15.0 (12.0-30.0)	< 0.001
Stem cell transplantation	59 (17.7%)	7 (77.8%)	< 0.001

SM: second malignancy

Table 7. Multivariable analysis for occurrence of second malignancy

		Multivariate			
	Variables	**OR**	**LCL**	**UCL**	**P-value**
Reoperation	No (reference)	1			0.027
	Yes	6.72	1.24	36.29	
Etoposide	(continuous value)	1.00	1.00	1.00	0.619
Carboplatin	(continuous value)	1.00	1.00	1.00	0.894
Cyclophosphamide	(continuous value)	1.00	1.00	1.00	0.696
Ifosfamide	(continuous value)	1.00	1.00	1.00	0.646
Radiotherapy	No (reference)	1			0.070
	Yes	4.95	0.88	27.91	
Stem cell transplantation	No (reference)	1			0.026
	Yes	7.38	1.27	42.97	

OR: odds ratio, LCL: lower confidence limit, UCL: upper confidence limit

Legends of figure

Figure 1. Flow chart for patient selection. During the study period, 792 operations were identified as abdominal tumor operations. Pathologic review revealed an additional three appendectomies as tumor operations.

Figure 2. Cumulative incidence of second malignancies. The 5-year and 10-year incidence rates are 1.2% and 7.3%, respectively.

Figure 3. Incidence of second malignancy according to clinical factors, 5-year and 10-year incidence rates. A. Reoperation (-): 0%, 3.4%, reoperation (+): 4.5%, 20.3% ($p < 0.001$). B. Chemotherapy (-): 0%, 3.8%, chemotherapy (+): 1.7%, 9.1% ($p = 0.579$). C. Radiotherapy (-): 0.4%, 0.4%, radiotherapy (+): 3.8%, 23.2% ($p = 0.001$). D. Stem cell transplantation (-): 0%, 1.8%, stem cell transplantation (+): 6.2%, 29.6% ($p < 0.001$). E. Resection margin 0: 0, 3.6%, 1: 0, 0%, 2: 1.7, 16.7% ($p = 0.349$).

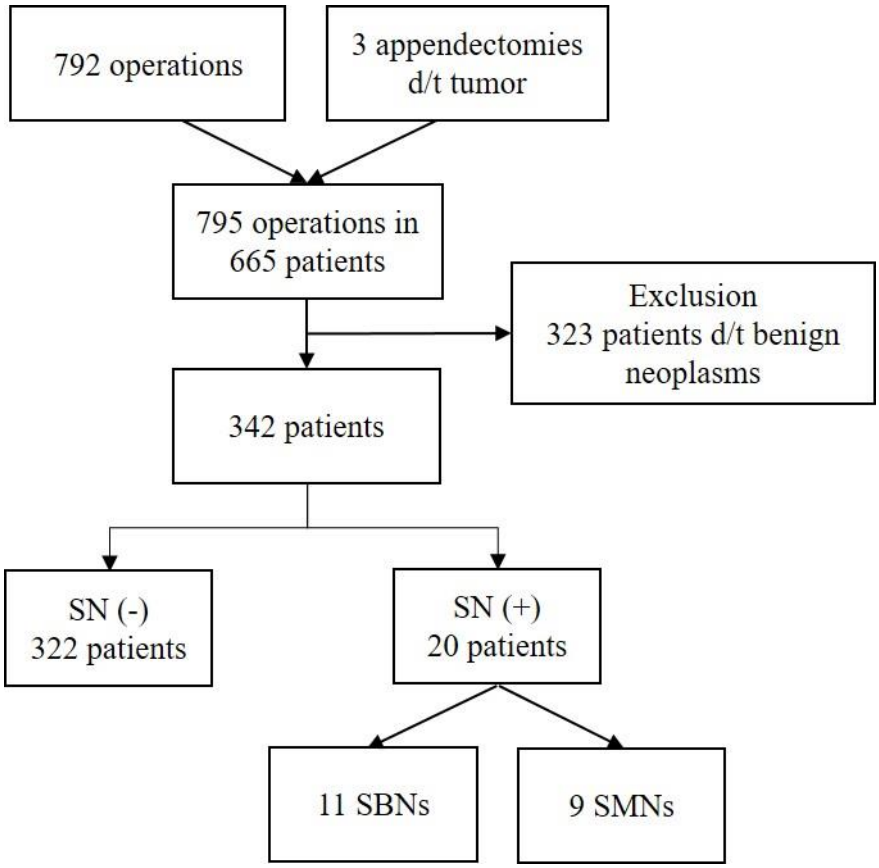
Figure 4. Comparison of survival between second and non-second malignancies, 5-year and 10-year overall survival rates. Second malignancy (-): 80.1%, 77.9%, second malignancy (+): 87.5%, 50.0% ($p = 0.487$).

Figure 5. Comparison of survival between second malignancies and second benign neoplasms, 5-year and 10-year overall survival rates. Second benign neoplasm: 100%, 100%, second malignancy: 87.5%, 50% ($p = 0.041$).

Figure 6. Incidence of second neoplasms according to neuroblastoma risk group, $p < 0.001$.

Figure 7. Incidence of second malignancies according to neuroblastoma risk group, $p = 0.119$.

Figure1. Flow chart for patient selection



SN: second neoplasm, SMN: sSecond malignant neoplasm, SBN: second benign neoplasm

Figure 2. Cumulative incidence of second malignancies

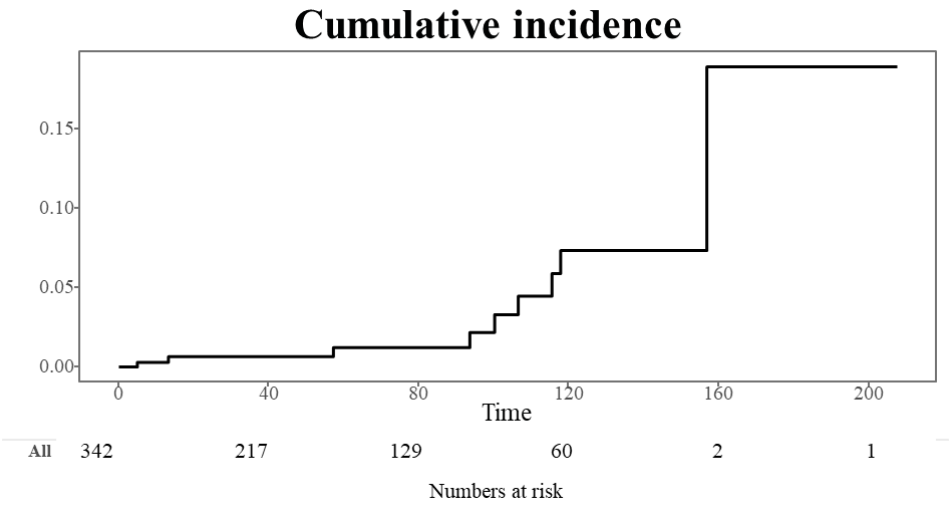
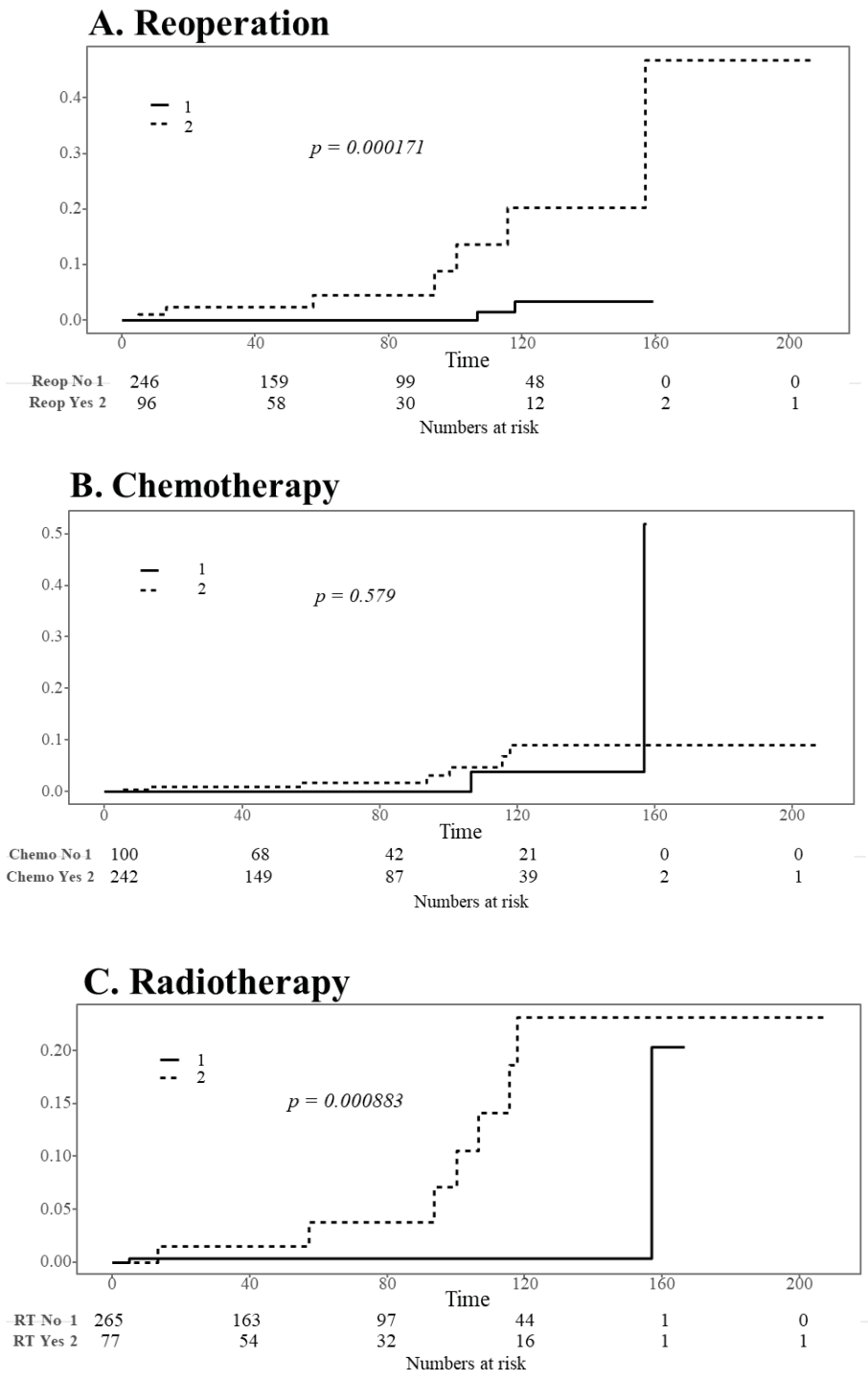
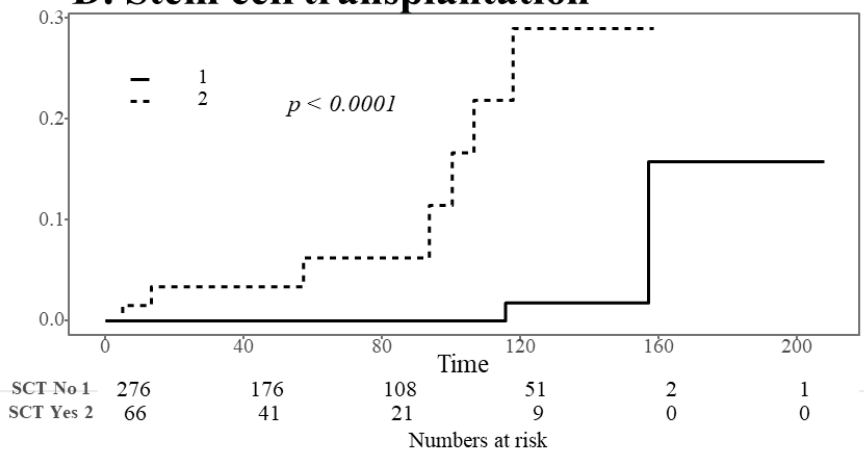


Figure 3. Incidence of second malignancies according to clinical factors



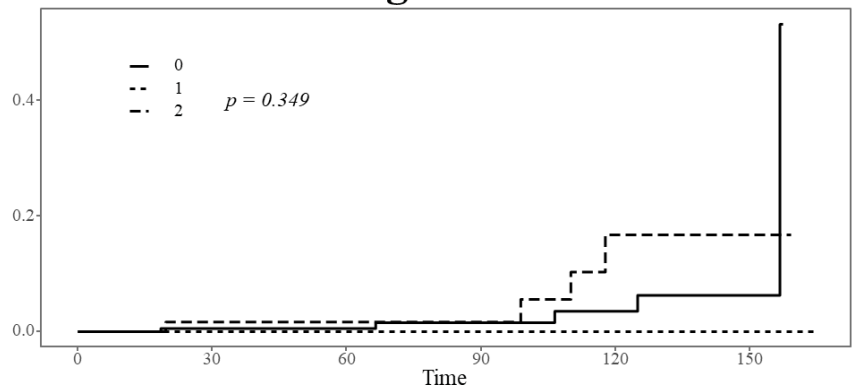
D. Stem cell transplantation



SCT No 1	276	176	108	51	2	1
SCT Yes 2	66	41	21	9	0	0

Numbers at risk

E. Resection margin



RM 0	216	153	111	65	40	12
RM 1	43	28	19	13	9	4
RM 2	82	55	39	28	12	5

Numbers at risk

Figure 4. Comparison of survival between secondary and non-secondary malignancies

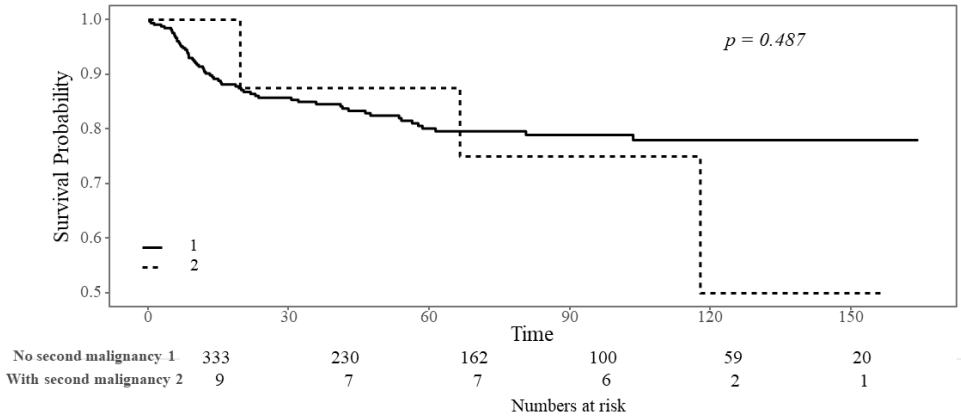


Figure 5. Comparison of survival between second malignancies and second benign neoplasms

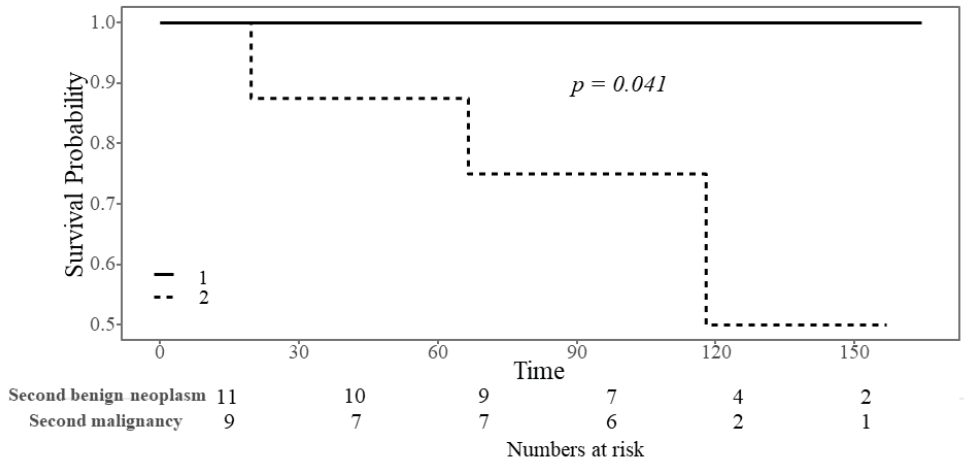


Figure 6. Incidence of second neoplasms according to neuroblastoma risk group

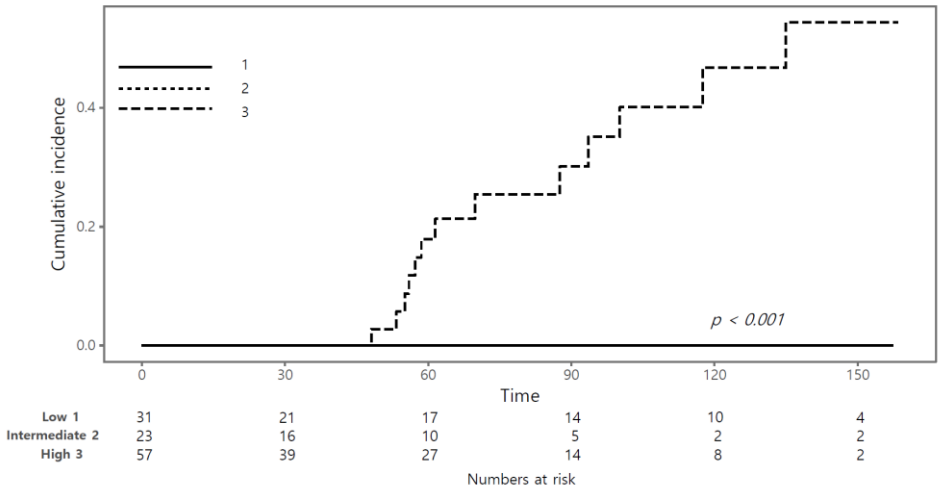
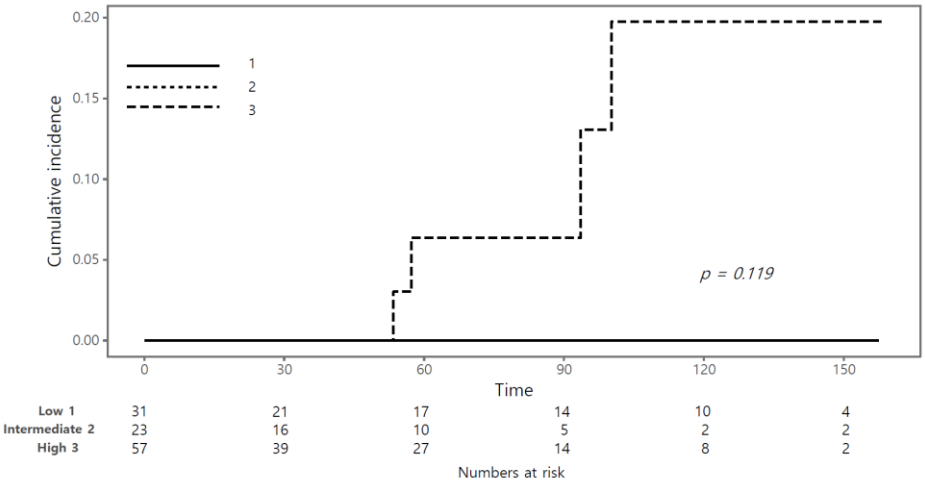


Figure 7. Incidence of second malignancies according to neuroblastoma risk group



요약

소아 복강 내 암으로 수술 받은 환자에서 발생한 이차 암의 위험 인자 분석

배경: 1차암 치료 후 2차 암의 발생에 관한 연구는 많이 있었지만 복부 악성 종양으로 수술을 받은 소아환자의 2차 암 발생에 관한 연구는 거의 없다.

방법: 본 연구는 2005년 1월부터 2017년 12월까지 서울대어린이병원에서 복부 악성 종양으로 진단받고 수술을 받은 환자 342명을 대상으로 후향적으로 수행한 연구로 2차 암 발생의 위험 인자를 조사했다. 연령, 성별, 진단, 수술 관련 요인 등 기본적인 환자 특성과 항암제 투여량, 방사선치료, 줄기세포이식 등의 치료와 관련된 요인을 조사했다. 두 군간의 비교는 적절한 방법과 다변량 Cox 회귀분석을 이용해 통계분석을 수행했다. 0.05보다 낮은 P값을 통계적으로 유의한 것으로 간주하였다.

결과: 환자 342명 중 2차 암이 발생한 환자는 9명이었다. 1차 암 수술 당시 중앙 연령은 3.9세, 남성은 193명(56.4%)이었다. 1차 암에 대한 가장 흔한 진단은 신경모세포종으로 110명 (32.1%)이었다. 2차 암의 예로는 신경모세포종 치료 후 신장암과 급성 골수성 백혈병 등이 있었다. 2차 암이 발생한 군과 그렇지 않은 군과 비교했을 때 유의한 요인은 재수술, 방사선 치료, 항암 치료, 조혈모 세포 이식, 그리고 시스플라틴, 에토포사이드, 사이클로포스파마이드와 같은 일부 항암제였다. 다변량 분석에서 재수술과 조혈모 세포 이식은 2차 암 발생에 유의한 요소였다. 전체 환자의 5년 생존율은 80.3% 였다. 생존율을 2차 암 발생별로 비교했을 때 5년 생존율은 유의한 차이는 없었다. (2차 암 87.5%, 비 2차 암 80.1%, p=0.487).

결론: 재수술과 조혈모 세포 이식이 복부 악성 종양으로 수술을 받은

소아 환자의 2차 암 발생과 관련이 있었다. 재수술과 조혈모 세포 이식 받은 소아 복부 종양 환자에 대해서는 장기적으로 면밀한 관찰과 관련된 지침이 필요하다.

주요어: 복부 종양, 소아, 이차 암, 방사선 치료, 항암 치료, 조혈모 세포 이식