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PORTAL HYPERTENSION IN CHILDREN WITH WILMS TUMOR: A REPORT FROM THE NATIONAL WILMS TUMOR STUDY GROUP

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Abstract

Purpose—This analysis was undertaken to determine the cumulative risk of and risk factors for portal hypertension (PHTN) in patients with WT.

Methods—Medical records were reviewed to identify cases of PHTN identified with late liver/spleen/gastric toxicities in a cohort of 5,195 patients treated on NWTs 1-4. A nested case-control study (5 controls/case) was conducted to determine relationships among doxorubicin, radiation therapy (RT) dose to the liver, patient gender and PHTN. Conditional logistic regression was used to estimate adjusted hazard ratios (HR) of PHTN associated with these factors.

Results—Cumulative risk of PHTN at 6 years from WT diagnosis was 0.7% for patients with right-sided tumors vs. 0.1% for those with left-sided tumors ($p=0.002$). Seventeen of 19 cases were evaluable for RT. The majority of cases (16/17, 94%) received right flank RT either alone or as part of whole abdomen RT and received > 15Gy to the liver. Fifteen of 17 (88%) patients received a higher dose to the liver than they would in modern WT protocols. Controlling for RT dose, the HR was 3.0 for patients who received doxorubicin ($p=0.32$) and 2.8 for females ($p=0.15$). Controlling for doxorubicin, the 95% lower confidence bound on the HR associating PHTN with a minimum liver RT dose >15 Gy vs. ≤15 Gy was 2.5 ($p=0.001$); it was 2.4 for a maximum liver dose >15 Gy vs. ≤15 Gy ($p=0.001$).

Conclusions—There was a strong association between higher doses of liver RT (>15 Gy) and the development of PHTN among WT patients.

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Keywords

Wilms tumor; portal hypertension; late-effects; radiation therapy; chemotherapy

INTRODUCTION

Wilms tumor, or nephroblastoma, is a tumor of the kidney that is relatively common in childhood, comprising 55% of all abdominal tumors and 6% of all cancers in children. It affects approximately one child in 10,000 in North America, and occurs most often between the ages of 1 to 5, with a roughly equal distribution between the sexes (1,2).

Management of this cancer depends on the stage of disease at diagnosis, the histologic subtype of the tumor, and the presence or absence of loss of heterozygosity (LOH) at 16q or 1p. Standard treatment consists of chemotherapy with or without radiation therapy to areas of unresectable disease. The most commonly used drugs have been vincristine, actinomycin D (AMD), and doxorubicin (3).

As survival for patients with Wilms tumor (WT) improves, more late effects and complications of therapy are noted. Long term side effects associated with this disease are mostly related to the treatments used. Scoliosis and soft tissue underdevelopment may occur as a result of irradiation. Likewise, second malignant neoplasms occur mainly in radiated areas. Cardiac dysfunction may occur in patients who receive either doxorubicin or chest irradiation, or both (4-6).

AMD is known to have a potential for liver damage, although little has been reported as a late effect of treatment (7). In addition, radiation to the liver, which may be delivered during irradiation of the right renal bed or the lung, has been shown to cause changes in the hepatic circulation and enlargement of the spleen similar to that seen with portal hypertension (8). Doxorubicin can exacerbate late toxicities related to radiation (6).

The circulation of blood in the liver is unique. All other organs in the body are perfused by blood arriving from the heart in arteries and going back to the heart in veins. One third of the blood perfusing the liver is arterial blood arriving via the hepatic artery, while two thirds is venous blood from the portal vein. The portal venous system is formed by the confluence of veins from the small and large intestine and the spleen. Portal hypertension (PHTN) represents an increase in pressure in the portal vein or one of its tributaries. It is manifested clinically by the development of splenomegaly and portal-systemic collaterals (e.g., *caput medusae*) that may result in gastric and esophageal varices. It can lead to severe gastrointestinal bleeding and may be fatal (9).

Portal hypertension is a rare complication observed after multimodality therapy for children with Wilms tumor. In 1971 Roback *et al.* reported a case of PHTN in a child with a right sided WT treated with AMD and radiation therapy (10). In 1986 Barnard *et al.* presented a similar case (11). Both Roback and Barnard proposed the combination of AMD and radiation therapy as a probable cause for the development of PHTN in these two children. In 1995, Warwick and co-workers followed two patients with right sided WT, both of whom developed PHTN. Both received AMD and radiation therapy following resection of their tumor. One had splenomegaly for years before developing symptoms of spleen and liver dysfunction; the other developed *caput medusae*, gastric and esophageal varices within months of diagnosis and had several episodes of severe gastrointestinal bleeding.

Roback and Barnard both recommended further study to determine the prevalence and range of severity of the portal hypertension in patients with Wilms tumor. The goal of this study was to determine the prevalence of and risk factors for PHTN in patients with WT.

METHODS AND MATERIALS

The population base was a cohort of patients entered in the randomized or followed categories of National Wilms Tumor Studies (NWTs) 1-4 during 1969-1991. The criteria used to select subjects were known date last seen, RT status known (whether given or not) and checklist available, known side of tumor, known final regimen and central histology. There were 5195 patients who met these criteria. Records for all patients with any late GI toxicity recorded prior to 1995 were reviewed (ABW) to identify cases of PHTN. (After 1995, due to funding cutbacks, systematic recording of late effects was limited to second malignant neoplasms, congestive heart failure, end-stage renal disease, and pulmonary complications.) Inclusion criteria were splenomegaly, esophageal and/or gastric varices, *caput medusae*, or a clinical diagnosis of PHTN. Exclusion criteria were acute veno-occlusive disease of the liver, viral hepatitis, recurrent or new malignant disease, or transient hepatopathy.

The cumulative risk of PHTN was estimated as one minus the Kaplan-Meier curve (12). Differences in risk between patient subgroups were evaluated using the log-rank test (13). A nested case-control study was conducted to determine how radiation therapy (RT) to the liver, doxorubicin and gender affected the relative risk of PHTN (14). Five matched controls were randomly selected for each case of PHTN from among subjects on the same study (NWTs-1,2,3, and 4) who were alive and under observation for at least as many days past WT diagnosis as it took for the case to be diagnosed. A reference date was defined for each case as the date of diagnosis of portal hypertension. Reference dates for matched controls were determined by adding the elapsed days until diagnosis of the case to their date of WT diagnosis. Only radiation therapy received before the reference date was considered in the calculation of cumulative amounts of radiation received to any particular organ.

Estimates of the possible range (minimum and maximum) of the total RT dose to the liver were calculated for each patient from the radiation therapy records. All RT charts and doses were verified by a radiation oncologist (JAK). The minimum RT dose was the estimated minimum dose received by the liver for a given set of irradiation fields for a patient. The maximum RT dose included the cumulative dose of any radiation to the liver from flank/abdominal/hepatic irradiation and from any other radiation field that may have been used such as whole lung irradiation (WLI) or irradiation fields for recurrent disease in the lung or abdomen. Detailed three-dimensional (3D) dosimetric assessments of liver doses from the different RT fields could not be performed as such data were not available. Statistical analyses were carried out for the maximum and minimum liver doses separately.

We considered portal hypertension as the outcome variable. Hazard ratios were estimated as odds ratios in 2 by 2 tables stratified by matched set, which is equivalent to conditional logistic regression analysis for binary risk factors (15). The effects of doxorubicin, liver RT dose and gender on PHTN risk were examined. For analysis purposes, we dichotomized both minimum and maximum RT dose as ≤ 15 Gy ("low" dose) or > 15 Gy ("high" dose). This dose (15 Gy) was used as it represented the division between RT doses more typically recommended in modern Wilms tumor protocols (flank RT doses of 0-10.8 Gy) and the higher doses (flank RT doses of 18-40 Gy) that were used in earlier NWTs protocols. Adjustments for other risk factors were made by further stratification on those factors. Due to the small sample size, we used exact methods to determine 95 % confidence limits (CI) and p-values for the adjusted hazard ratios (16).

RESULTS

Patient population

Nineteen cases of PHTN were identified among the 5195 patients. All occurred within 6 years of WT diagnosis. The cumulative risk at 6 years for patients with left sided tumors (3 cases) was approximately 0.1% whereas for right sided tumors (15 cases) it was 0.7% (Figure 1, $p=0.002$). Among patients with bilateral disease, a single case of PHTN occurred in a patient who had a right nephrectomy with irradiation of the fossa and wedge resection of two small foci of WT in the left kidney.

Seventeen of 19 identified cases were evaluable for analysis of RT effects. Thus there were 17 matched sets consisting of 1 case and 5 controls each for a total of 102 patients in the sub-study. Table 1 summarizes the demographic and diagnostic information for cases and controls. Fourteen cases, including the single bilateral case, had WT involving the right kidney. Twelve were female. Most cases were Caucasian and over 80% had favorable histology. On average, controls were about one year younger than cases. Among cases there were more females, but among controls females and males were distributed evenly. The final stages for most cases were II-IV; however, most controls were in stages I-III. No case relapsed before the reference date, but 11 of 85 controls did.

Table 2 contrasts treatments received by cases and matched controls. Fifty-three percent of cases but only 20% of controls received doxorubicin. All cases received both RT and AMD. In general, the PHTN cases had higher radiation doses to the liver than controls did, especially for those in the NWTS-3 and NWTS-4 studies. Since matching of cases and controls was not accounted for, no inferential statistical analyses were conducted of the frequencies shown in Table 2. All 17 patients were treated either with Cobalt-60 gamma rays (4 patients) or 4-6MV x-rays (13 patients). The RT dose per fraction ranged from 1.5-2 Gy. The details of the RT fields and dosages received by the patients with portal hypertension are shown in Table 3. Sixteen of 17 (94%) cases received a liver dose > 15 Gy. The mean liver dose and the range of minimum and maximum liver doses are shown. The majority of cases (16/17, 94%) received right flank RT either alone or as part of whole abdomen RT. The only patient who received left flank RT also received liver RT later. Fifteen of 17 (88%) patients were judged to have received a higher dose to the liver compared to doses they would have received on modern Wilms tumor protocols.

Hazard ratios

Results of the exact statistical analyses of the matched data are presented in Table 4. The wide confidence limits on HRs show the statistical limitations of a study with only 17 cases. By chance, the only case who did not receive more than 15 Gy RT was matched to 5 controls who received no RT at all to the liver. Thus the point estimate and upper confidence limit for the HR comparing RT doses above 15 Gy with doses of 15 Gy and below were both infinite. The lower confidence limits suggest that higher (>15 Gy) liver dose increased the hazard by at least 4.7 fold, whether the evaluation was based on minimum or maximum estimated dose ($p < 0.0001$). Adjustment for the fact that patients who received higher dose RT were substantially more likely also to receive doxorubicin reduced the lower confidence limit, but it remained well above 2 and the result was still statistically significant ($p < 0.002$). Controlling for doxorubicin, the 95% lower confidence bound on the HR associating PHTN with a minimum liver RT dose >15 Gy vs. ≤ 15 Gy was 2.5 ($p=0.001$); it was 2.4 for a maximum liver dose >15 Gy vs. ≤ 15 Gy ($p=0.001$). By contrast, adjustment of the doxorubicin HR for the association with higher dose RT brought the lower confidence limit below one ($p=0.32$). The hazard ratio estimated for female gender was 2.8, but was not statistically significant regardless of adjustment for the treatment variables.

DISCUSSION

This report indicates the presence of a strong association between higher liver radiation doses and the development of PHTN in Wilms tumor patients. As all cases and controls received AMD, it was not possible to assess its effect. The small dataset had limited power to analyze the possible contributions of doxorubicin or gender.

A number of pathophysiologic changes have been reported to occur following irradiation of the liver (17-19). Liver irradiation in children initially results in hyperemia and hepatic cell loss near the center of the hepatic lobules caused by obliterative changes in the small branches of the hepatic veins similar to veno-occlusive disease. These changes can be observed within 3 months after irradiation. This is followed by paracentrilobular fibrosis and mild portal fibrosis. The liver hyperemia and cell loss are reversible due to the development of collateral vessels; however, the pathologic changes in the small veins persist (17). Higher doses of RT (>30 Gy) to the liver in children have been shown to cause sclerosis of the hepatic sinusoids, portal veins and hepatic arterioles resulting in pathologic and functional outcomes similar to nodular cirrhosis. Thrombocytopenia during the acute phase (six months) after hepatic irradiation was also more common after higher doses of liver irradiation to major volumes of the liver (>35 Gy) (18,19). Clinical signs of hepatic congestion and splenomegaly with or without hypersplenism have been reported following right-sided flank irradiation that would routinely include a major portion of the right-lobe of the liver in children with Wilms tumor or neuroblastoma. Acute portal venous congestion resulting from back-pressure caused by the swollen hepatic parenchyma was postulated to be the cause for splenomegaly and hypersplenism. However, the persistence of splenomegaly in many children 1-2 years after irradiation suggested that this may also be related to the long-term alteration in the dynamics of the portal circulation caused by fibrosis and compensatory enlargement of the left lobe of the liver (20,21).

To our knowledge there are only three published case reports on the occurrence of portal hypertension after Wilms tumor therapy. All of these patients were girls and had RT fields that included a significant portion of the liver (right-sided tumors) to high doses of RT (20-50 Gy). Roback et al. described the development of portal hypertension in a 4.5 year old girl after surgery, chemotherapy (AMD, vincristine) and three separate courses of RT (34.95 Gy to the right abdomen, 14.12 Gy to both lungs and 14 Gy to a part of the lung). Three months after surgery, a liver scan demonstrated a reduced uptake in the irradiated portion of the liver and there were signs of increased portal venous pressure (splenomegaly and thrombocytopenia). A liver biopsy revealed mild periportal fibrosis and mononuclear cell infiltrate. Two years after her nephrectomy she developed portal hypertension with splenomegaly and life-threatening hematemesis from esophageal varices. Her portal pressure normalized following a mesocaval shunt. Liver biopsies revealed pathologic changes similar in appearance to those observed at 3 months. The contributory factors for portal hypertension were liver irradiation by flank and lung irradiation portals and potentiation of radiation effects by AMD. Veno-occlusive disease at the post sinusoidal level was implicated as the cause of portal hypertension. The authors also report having observed signs of portal hypertension with hepatosplenomegaly and hypersplenism without esophageal varices in four other children with right sided Wilms tumor following flank and lung irradiation (10). Barnard et al. described a 9 year old girl, with a right-sided Wilms tumor who was treated with surgery, chemotherapy (vincristine and AMD for 16 months) and RT (20 Gy) to the renal bed. Twenty-six months after surgery she presented with hematemesis and signs of portal hypertension including splenomegaly, esophageal and gastric varices. Liver biopsy showed the presence of periportal fibrosis with multiple areas of narrowing or obliteration of interlobular portal veins. The central veins were patent. These histopathologic features were considered distinct from veno-occlusive disease due to the presence of patent central veins but rather typical of non-cirrhotic portal fibrosis. A distal

splenorenal shunt was performed and the child had no further recurrence of variceal bleeding (11).

Thomas et al. reported a girl with a right-sided Wilms tumor who was initially treated with nephrectomy, whole abdomen RT (21.35 Gy) followed by a right flank boost (15 Gy) that included a portion of the liver and chemotherapy with vincristine and AMD for 15 months. She developed hematemesis and esophageal varices secondary to portal hypertension 4.5 years after treatment. Liver biopsy revealed sclerosis of the central veins with focal translobular sinusoidal fibrosis and regenerating nodules. The patient had spontaneous resolution of symptoms without surgery (19).

As described in the report by Roback et al. (10), an important RT-related factor that could impact on the volume of normal liver irradiated was the sequence of flank/abdominal RT and lung RT in children who required both. It has been generally recommended in NWTS protocols that both flank and chest be irradiated simultaneously when indicated. However, in certain situations when lung metastases develop later in the course of the disease, the whole lung RT portal would re-irradiate significant portions of the liver that were previously included in the flank RT field. The total liver dose received from these RT fields and the liver volume irradiated to such doses becomes an important contributor to the development of late toxicities such as PHTN when higher flank RT doses were delivered as in earlier NWTS protocols (Figure 2,3) (Table 3). This factor was taken into account while estimating the maximum and minimum liver doses received in this study.

Evolution of Radiation-therapy (RT) guidelines in NWTS protocols

The indications for and dosages of flank/abdominal RT in children with Wilms tumor enrolled on NWTS protocols have undergone considerable changes over time, with children treated in the modern era receiving significantly lower doses of RT (Fig 2,3). In NWTS-1 and -2, all group II-IV tumors and a subset of group I tumors received flank RT to doses ranging from 18 Gy to 40 Gy based on an age-adjusted dose regimen. Presently, among favorable histology tumors, only children with stage III tumors receive flank RT to a dose of 10 Gy with 3 drug chemotherapy. Likewise, whole lung RT was recommended for all children with lung metastases to a dose of 12-14 Gy in NWTS-1 and part of NWTS-2. However, in NWTS 3-5, lung RT to a dose of 12 Gy was recommended for those favorable histology tumors with overt lung metastases visible on chest x-ray. In children with small lung metastases visible only on CT scans, whole lung RT was not mandatory (22-24). Similarly, the RT dose recommended for children with liver metastases was reduced from 30Gy in earlier NWTS protocols to 19.8 Gy in most modern Wilms tumor protocols (22-24). Earlier NWTS protocols used 2-D RT planning and pre-operative excretory urograms to define RT fields. However, most modern Wilms tumor protocols recommend the use of CT-simulation, 3-D treatment planning and pre-operative CT-based tumor volumes to define RT fields. All these measures will ensure the delivery of a more homogeneous dose to the target tissues while permitting superior protection of normal tissues such as liver in children treated on modern WT protocols.

Evolution of Chemotherapy guidelines in NWTS protocols

The drugs used and indications for their use in children with Wilms tumor have likewise changed over time, with children treated currently receiving, in general, lower cumulative doses of drugs, and treatment over a shorter period of time. In NWTS-1, the combination of vincristine and AMD was found to be better than either drug alone for children with stage II or III favorable histology (FH) disease (25). In NWTS-2, six months of vincristine and AMD were found to be sufficient for children with stage I FH disease, while the addition of doxorubicin increased relapse-free survival for children with stage II or III FH disease (26). Therapy reduction proved possible in NWTS-3: 11 weeks of two drug therapy was sufficient

for stage I FH disease, while doxorubicin (and RT) were shown to be necessary only for stage III FH disease. In NWTs-4, further reduction was shown to be effective: overall length of therapy decreased from around 15 months to 6 months, reducing the overall dose exposure to chemotherapy, especially for AMD and doxorubicin. In addition, “pulse-intensive” drug administration (single doses of drug, e.g., AMD or doxorubicin, administered on one day instead of divided over several days) decreased the number of days a child received drug, and also reduced the toxicity associated with those drugs (27,28). Presently, among children with FH tumors, doxorubicin is given initially only to children with stage III and IV disease, or those with stage II disease whose tumors show loss of heterozygosity at both 1p and 16q – shown in NWTs-5 to be associated with a poorer outcome (29).

The risk of PHTN reported here, from 0.1% to 0.7% at 6 years depending on side of tumor based on 19 patients identified from a cohort of over 5000, is likely to be an underestimate for several reasons. First, PHTN is frequently a “silent” disease, with symptoms occurring and diagnosis made only when the pathophysiology is far advanced. Second, the treatment protocols made no specific request for routine reporting of PHTN in follow-up records whose primary purpose was to document recurrence of WT. Patients may not think to inform their pediatric oncologist regarding new medical diagnoses. The 19 cases identified by no means represent a complete census of all cases of PHTN following WT diagnosed in North America; coverage by the NWTs was limited, particularly during the early years. Two such patients followed by Warwick and coworkers were never registered on NWTs and hence did not contribute to this analysis. Furthermore, there was no overlap between the cases reported here and the cited literature.

CONCLUSIONS

This is the largest report on the occurrence of portal hypertension after Wilms tumor therapy and adds to the scant literature on this subject. The strong association between higher liver radiation doses delivered during right-sided flank RT, either alone or following abdomen/lung/liver RT, and portal hypertension has been further confirmed in this study. The small data set had limited power to analyze the possible contributions of doxorubicin and gender. The exact pathogenesis of treatment-induced portal hypertension remains to be clearly defined. In Wilms tumor survivors treated in the modern era, there would likely be fewer cases of portal hypertension due to the significant reduction in the indications for and dosages of RT and the reduced intensity of chemotherapy. Close, long-term follow-up of cancer survivors is needed to identify this and other late effects of therapy.

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Figure 1. Cumulative risk of portal hypertension among patients with WT in the left kidney, right kidney or both kidneys.

Figure 2.

Digitally Reconstructed Radiographs (DRRs) of a child showing RT doses delivered to the lungs, liver and right flank following sequential treatment with flank RT and whole lung RT. a (left): Modern NWTs protocol doses of Flank RT (10.8 Gy) and Whole lung RT (12Gy). b (right): Earlier NWTs protocol doses of Flank RT (34.2 Gy) and Whole lung RT (12 Gy). Note the overlap of doses from the two fields over the liver.

Figure 3.
Liver Dose-Volume histograms (DVHs) for the two clinical situations described in Fig. 2a and b.

Table 1

Case-control comparison of demographic and prognostic variables

		Case N (%)	Control N (%)
Total		17	85
Mean age (years)		4.7	3.5
Race	Caucasian	15 (88.2)	63 (74.1)
	African American	2 (11.8)	13 (15.3)
	Hispanic	0 (0)	7 (8.2)
	Unknown	0 (0)	2 (2.4)
Gender	Male	5 (29.4)	43 (50.6)
	Female	12 (70.6)	42 (49.4)
Final Stage	I	1 (5.9)	33 (38.8)
	II	6 (35.5)	30 (35.3)
	III	6 (35.5)	13 (15.3)
	IV	3 (17.6)	6 (7.1)
	V	1 (5.9)	3 (3.5)
Histology	Favorable	14 (82.4)	74 (87.1)
	Focal Anaplasia	0 (0)	1 (1.2)
	Diffuse Anaplasia	1 (5.9)	2 (2.4)
	Clear Cell Sarcoma	1 (5.9)	0 (0)
	Rhabdoid Tumor	0 (0)	1 (1.2)
	Other	1 (5.9)	7 (8.2)
Study	NWTS-1	5 (29.4)	25 (29.4)
	NWTS-2	6 (35.3)	30 (35.3)
	NWTS-3	3 (17.6)	15 (17.6)
	NWTS-4	3 (17.6)	15 (17.6)

Table 2

Case-control comparison of treatment variables

		Case N(%)	Control N(%)
Total		17	85
Chemotherapy	A	0 (0)	10 (11.8)
	V	0 (0)	4 (4.7)
	A+V	8 (47)	55 (64.7)
	A+V+D	8 (47)	15 (7.6)
	A+V+D+C	1 (5.9)	1 (1.2)
Minimum RT dose to liver (Gy)	0	0 (0.0)	36 (42.4)
	(0, 15)	1 (5.9)	8 (9.4)
	(15, 25)	7 (41.1)	17 (20.0)
	> 25	9 (52.9)	24 (28.2)
Maximum RT dose to liver (Gy)^a	0	0 (0.0)	36 (42.9)
	(0, 15)	1 (5.9)	6 (7.1)
	(15, 25)	5 (29.4)	8 (9.5)
	> 25	11 (64.7)	34 (40.5)
Mean RT dose to liver (Gy)		Min / Max	Min / Max
	NWTS-1	29.7 / 32.2	21.5 / 28.5
	NWTS-2	26.2 / 35.5	19.8 / 22.5
	NWTS-3	23.3 / 23.3	5.8 / 8.3
	NWTS-4	21.4 / 21.4	1.4 / 1.4

^aOne control had a "missing value" for maximum RT dose, and was not used for analyses of maximum RT dose.

Table 3
Radiation therapy (RT) fields and dosages received by patients with portal hypertension

RT Fields	# of Patients	Minimum Liver Dose Mean (Range)	Maximum Liver Dose Mean (Range)	# Patients receiving higher than modern RT doses
Right Flank only	10 (59%)	28.2Gy (19.8-40Gy)	28.2Gy (19.8-40Gy)	10/10
Right Flank + RT to Bone/Lung/Nodes	3 (17%)	25.9Gy (18-33.6Gy)	40Gy (33.6-47.5Gy)	3/3
Left Flank+ RT to Liver	1 (1%)	30Gy	40.5Gy	1/1
Whole Abdomen only	1 (1%)	10.8Gy	10.8Gy	0/1
Whole Abdomen + RT to Right Flank/Liver	2 (12%)	19.8Gy	27.6Gy (19.8-35.4Gy)	1/2

Table 4

Summary of exact hazard ratio (HR) analyses

Comparison groups	HR	95% CI	<i>p</i> -value	Adjustment factors
Minimum RT dose >15 vs. ≤15 Gy	∞	(4.8, ∞)	<0.0001	Matched set
Minimum RT dose >15 vs. ≤15 Gy	∞	(2.5, ∞)	0.0013	Matched set + Doxorubicin
Maximum RT dose >15 vs. ≤15 Gy	∞	(4.7, ∞)	<0.0001	Matched set
Maximum RT dose >15 vs. ≤15 Gy	∞	(2.4, ∞)	0.0014	Matched set + Doxorubicin
Doxorubicin vs. No doxorubicin	9.3	(1.7, 91)	0.005	Matched set
Doxorubicin vs. No doxorubicin	3.0	(0.5, 33)	0.32	Matched set + RT
Female vs. male gender	2.8	(0.8, 12)	0.15	Matched set