Risk-adapted treatment reduced chemotherapy exposure for clinical stage 1 pediatric testicular cancer

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Abstract

Background: Different from adult clinical stage I (CS1) testicular cancer, surveillance was recommended for CS1 pediatric testicular cancer. For high-risk children, greater than 50% of them suffered relapse and progress during surveillance and adjuvant chemotherapy was administrated. Risk-adapted treatment might reduce chemotherapy exposure for those children.

Methods: The decision model was designed and calculated using TreeAge Pro 2011 software. Clinical utilities such as relapse rates of different groups during surveillance or after chemotherapy were collected from literatures. And a survey to urologist was performed to evaluate the toxicity of the first-line and second-line chemotherapy. Using decision analysis model, chemotherapy exposure between risk-adapted treatment and surveillance were compared based on this series of clinical utilities. One-way and two-way tests were administrated to check the feasibility.

Results: In base case decision analysis of CS1 pediatric testicular cancer, risk-adapted treatment preferred lower exposure of chemotherapy than surveillance (average: 0.7965 cycle verse 1.3419 cycles). The sensitivity analysis demonstrated that when relapse rate after primary chemotherapy ≤0.10 and the relapse rate of high-risk group ≥0.40, risk-adapted treatment would expose lower chemotherapy, without association of the proportion of low-risk patients, the relapse rate of low-risk group, relapse rate after salvage chemotherapy and toxicity utility of second-line chemotherapy compared to first-line chemotherapy.

Conclusions: Using decision analysis, risk-adapted treatment might decrease chemotherapy exposure for these high-risk patients and precious evaluation after orchiectomy was critical to this process. Further clinical study was needed to validate this statement.

Background

Despite the low incidence of pediatric testicular tumors, yolk sac tumor is the most common malignant type in children, which is different from its adult counterpart.[1-6] And 70% to 80% patients have clinical stage Ⅰ (CS1) disease, for its hematogenous predilection of metastasis in children, primary retroperitoneal lymph node dissection (RPLND) was not recommended for CS1 yolk sac tumor.[1, 6-7] In the recent summary of PDQ Pediatric Treatment Editorial Board and recommendation of POG/CCG, surveillance was recommended for children with CS1 testicular cancer after radical inguinal orchiectomy (RIO).[8-9]

In recent studies, about 20% of children with CS1 testicular germ cell tumors (GCT) suffered a relapse in 4 years after RIO and underwent 3-4 cycles of salvage chemotherapy.[1, 9] Advanced analysis demonstrated that age > 10 years, mixed histology and lymphovascular invasion (LVI) were associated with disease relapse.[10-11] And in high-risk children, more than 50% of them suffered relapse and progress.[6, 10] For their adult counterparts, risk-adapted management achieved a favorable outcome for CS1 testicular nonseminomatous germ cell tumors (NSGCT).[12-13] This procedure might also be feasible for pediatric

patients, and lower the exposure of chemotherapy, though the outcome was excellent with surveillance and salvage chemotherapy. However, no study was to compare the cost and toxicity between surveillance and risk-adapted management.

In this study, using a decision analysis model, we evaluated the chemotherapy burden of CS1 pediatric testicular cancer between risk-adapted treatment and surveillance.

Methods

The decision model was designed and calculated using TreeAge Pro 2011 software (http://www.treeage.com), and the decision tree of surveillance and risk-adapted treatment **and flowchart of analysis were listed in Figure 1 and 2**.

For these two groups, the cost of radical inguinal orchiectomy and regular follow-up was similar. And in China, the cost of operation, drugs, enrollment and etc was nearly consistent under legal regulations in the recent decade. Generally, chemotherapy toxicity was associated with the number of chemotherapy cycles. So we just compare the exposure of chemotherapy between the two groups. Our analysis consisted of the following hypothetical clinical scenarios for two groups: Firstly, patients in both groups with CS1 testicular cancer were diagnosed with histopathology, serum markers and imaging. Then, for the surveillance group, patients suffered relapse during follow-up and received salvage chemotherapy with 3 cycles of PEB (cisplatin, VP-16 and bleomycin) chemotherapy. If complete response (CR) was not achieved after 3 cycles of PEB, second-line chemotherapy with 3 cycles of VIP (VP-16, ifosfamide and cisplatin) was performed. For the risk-adapted group, the high-risk group received primary chemotherapy with 1 cycle of PEB, and low-risk group underwent surveillance. Then salvage chemotherapy with 3 cycles of PEB was performed when relapse was detected. If CR was not achieved after 3 cycles of PEB, second-line chemotherapy with VIP was performed. According to recent studies, the overall survival of CS1 pediatric testicular cancer was nearly 100% with system chemotherapy, and progression rates after primary and salvage chemotherapy both were about 5% (2.3-6.8%) (**Table 1**).[6, 9, 12, 14-20] And rare operation or radiation after chemotherapy was reported as guidelines recommended. Based on these studies, we defined relapse rates of high and low-risk patients who underwent surveillance were 0.60 (0.38-0.73) and 0.15 (0.10-0.20), respectively; the proportion of low-risk patients was from 0-1, progression rates after primary and salvage chemotherapy were both 0.05 (0.01-0.10), and second line chemotherapy was the last treatment with a 100% success rate (as shown in **Figure 2** and **Table 1**).[6, 9, 12, 14-20]

To evaluate treatment-related toxicity between first-line and second-line chemotherapy, digital values were obtained in an interview with urological oncologists. Before the interview, the consensus of short and long-term toxicity of chemotherapy for testicular cancer was acquired. By means of a visual analogue scale, compared to surveillance, values of salvage chemotherapy and second-line chemotherapy were assessed as 0.841 (95% confidence interval: 0.811-0.871) and 0.635 (95% confidence interval: 0.578-

0.697), respectively. So we defined the toxicity of second-line chemotherapy was about 0.814/0.635=1.3 times of those of salvage chemotherapy. And the range was defined as 1.0-2.0 in decision analysis.

Results

In all, 24 urologists and oncologists took part in the interview to evaluate toxicity of chemotherapy for pediatric testicular cancer. As shown in **Table 2**, compared to orchiectomy without chemotherapy (value=1.0), the value of first-line chemotherapy was from 0.682-1.000, and the value of second-line chemotherapy was from 0.435-0.960. The average number and standard deviation of them were 0.841 and 0.081, 0.635 and 0.151, respectively. And we defined the toxicity of second-line chemotherapy was about 0.814/0.635=1.3 times of those of salvage chemotherapy with range of 1.0-2.0 in decision analysis.

Our analysis demonstrated that risk-adapted treatment preferred lower exposure of chemotherapy than surveillance (average: 0.7965 cycle verse 1.3419 cycles).

1-way sensitivity analysis demonstrated that difference of chemotherapy exposure between two treatments was associated with the proportion of low-risk patients (pLowRisk): when pLowRisk =0, all patients are in high-risk group, and two treatments have significantly different exposure of chemotherapy; when pLowRisk =1, all patients are in low-risk group, and two groups have same exposure of chemotherapy (**Figure 3A**). Similarly, when the relapse rate of high-risk group (pRelapseHighrisk) ≥0.40 and relapse rate after primary chemotherapy (pRelapsePostPrimChemo) ≤0.25, risk-adapted treatment was associated with lower chemotherapy exposure (**Figure 3B, C**). And the risk-adapted treatment was associated with lower chemotherapy exposure without association with the relapse rate of low-risk group (pRelapseLowrisk), relapse rate after salvage chemotherapy (pRelapsePostSalvChemo) and toxicity utility of second-line chemotherapy compared to salvage chemotherapy (tSecondChemo)(**Figure 3D, E, F**). It means only pRelapseHighrisk and pRelapsePostPrimChemo were associated with the utility of chemotherapy exposure, so we focused on these two factors in 2-way sensitivity analysis.

In the 2-way sensitivity analysis, we found that when pRelapseHighrisk ≥0.40, risk-adapted treatment was associated with lower chemotherapy exposure without association of pLowRisk, pRelapseLowrisk, pRelapsePostSalvChemo and tSecondChemo (**Figure 4A,** Supplementary **Figure 1 A, B, C**). When pRelapsePostPrimChemo ≤0.25, pLowRisk ≤0.90, risk-adapted treatment was associated with lower chemotherapy exposure (**Figure 4B**). While, pRelapsePostPrimChemo ≤0.25, risk-adapted treatment would prefer lower exposure of chemotherapy without association of pRelapseLowrisk, pRelapsePostSalvChemo and tSecondChemo, too (**Figure 4C, D, E**). In the 2-way sensitivity analysis of pRelapseHighrisk and pRelapsePostPrimChemo, when pRelapsePostPrimChemo ≤0.10 and pRelapseHighrisk ≥0.40, risk-adapted treatment would expose lower chemotherapy (**Figure 4F**).

Discussions

For pediatric testicular cancer is nearly curable, surveillance is recommended for clinical stage 1 patients and salvage chemotherapy undergo when relapse disease is detected.[8-9] But in their adult counterpart, risk-adapted management acquired favorable outcome, and decision analysis demonstrated that surveillance was preferred intervention except for those patients with high risk for relapse.[12-13] Meanwhile, for extremely long survival time of these pediatric patients, treatment-related toxicity also should be taken into consideration.[21] In some studies, primary chemotherapy was associated with an extremely low relapse rate, and it decreased relapse rate in the high-risk group significantly.[6] So we used decision analysis to develop a model to evaluate the chemotherapy exposure between two protocols. Risk-adapted management might reduce the exposure of chemotherapy by primary chemotherapy for high-risk patients.

TreeAge Pro is the leading software for decision analysis, and the decision model was developed based on historical data from previous literature. Though this model is simple, the exposure of chemotherapy could be calculated clearly. And several prediction methods based on artificial intelligence seems effective, but clouds of data or lots of instruments are needed.[22-24] For this rare cancer, which was sporadic, big data was not available. So we choose a simple decision model only focused on chemotherapy exposure.

In this study, risk-adapted treatment exposed less chemotherapy than surveillance, which was not consistent with the clinical decision following current guidelines. In the 1-way sensitive analysis, only relapse rate of the high-risk group (pRelapseHighrisk) and relapse rate after primary chemotherapy (pRelapsePostPrimChemo) were associated with chemotherapy exposure. When pRelapseHighrisk $\geq$0.40 or pRelapsePostPrimChemo $\leq$0.25, risk-adapted treatment tied to lower chemotherapy exposure, meanwhile these two utilities were reasonable in clinical practice (**Figure 3**). Within 2-way analysis, when pRelapsePostPrimChemo $\leq$0.10 and pRelapseHighrisk $\geq$0.40, risk-adapted treatment would decrease chemotherapy exposure, without association of the other four factors.These results implied that the more precise stratification of the high-risk group and the higher CR rate of primary chemotherapy, the better individualized management would be accomplished, and less treatment-related toxicity would be exposed.

In recent studies, the rate of relapse was about 20% for CS1 pediatric testicular cancer, and most occurred in the first 2 years.[9] In limited series, the relapse rate of high-risk group was about 60%, and that of the low-risk group was 15%.[6, 9, 12, 14-20] And the rate of patients with primary chemotherapy was less than 5% and the overall survival rate was nearly 100%. In our prior study, the relapse rate was about 33% and the overall survival was 98%. Meanwhile, necrosis, the new predictor of tumor relapse, combined with LVI stratified patients into 2 groups, and the relapse rates were 73% and 17%, respectively.[6] In other studies, the relapse of high-risk group was 0.38-0.55, and the relapse of low-risk group was 0.16-0.19.[9, 12, 14-20] Based on these data, we evaluated that the chemotherapy exposure was lower in risk-adapted treatment in our model. For the favorable outcome of salvage chemotherapy for clinical stage 1 patients, primary chemotherapy was not common in these studies. However, some studies also demonstrated that primary

chemotherapy was associated with an extremely low relapse rate.[6] And in adult patients with CS1 testicular NSGCT, primary chemotherapy achieved an excellent oncological outcome and this procedure might also be effective in pediatric patients.[12-13]

Actually, based on the contemporary scenario, this study revealed that risk-adapted treatment was associated with less chemotherapy exposure significantly. And pRelapsePostPrimChemo and pRelapseHighrisk were significant factors to decrease exposure of chemotherapy, which implying that the effectiveness of primary chemotherapy and differentiation of high-risk patients were critical to individualized management. For primary chemotherapy, the outcome is favorable and lower-toxicity regimen might be available.[19] While in a recent study, the relapse rate of high-risk group was >70% with a combination of two high-risk factors (LVI and necrosis), and further research about prognostic markers was needed.[6] As precise management of cancers developed, the differentiation of testicular cancer boys would be more accurate and risk-adapted treatment would reduce chemotherapy exposure robustly.[25]

Our study had some limitations worth noting. To simplify the analysis of chemotherapy toxicity, we calculate cycles of chemotherapy instead of detailed side effects, such as cardiovascular disease, neurotoxicity, ototoxicity, chronic kidney disease, infertility, and etc. The proportions were defined according to recent studies, for it is minor populated, bias was presented, and some of them were from studies about adult counterparts. For shortage of life-long follow-up of this curable disease, quality-adjusted life-year and cost-effectiveness analysis were not performed in this study. Despite these shortages, we believe this model could imply some advantages of risk-adapted management in CS1 pediatric testicular cancer. And this is the first report regarding the chemotherapy burden in CS1 pediatric testicular cancer.

Conclusions

Our decision model of management for clinical stage 1 pediatric testicular cancer demonstrated that risk-adapted treatment was associated with lower exposure of chemotherapy. Further clinical study was needed to validate this statement.

Abbreviations

CS1: clinical stage

RPLND: retroperitoneal lymph node dissection

POG/CCG: Pediatric Oncology Group and Children's Cancer Group

RIO: radical inguinal orchiectomy

GCT: germ cell tumors

LVI: lymphovascular invasion

NSGCT: nonseminomatous germ cell tumors

PEB: cisplatin, VP-16 and bleomycin

CR: complete response

VIP: VP-16, ifosfamide and cisplatin

pLowRisk: proportion of low-risk patients

pRelapseHighrisk: relapse rate of high-risk group

pRelapsePostPrimChemo: relapse rate after primary chemotherapy

pRelapseLowrisk: relapse rate of low-risk group

pRelapsePostSalvChemo: relapse rate after salvage chemotherapy

tSecondChemo: toxicity utility of second-line chemotherapy compared to salvage chemotherapy

Declarations

Ethics approval and consent to participate

Due to the data was derived from literature, ethics approval and consent to participate was not applicable.

Consent to publish

Not applicable.

Availability of data and materials

The data was derived from literature as referred in manuscript.

Competing Interest

The authors declare that they have no competing interest.

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Authors' contributions

YLY, ZFC, JB and HTL were responsible for data collection and analysis, interpretation of the results, and writing the manuscript. JB and ZKQ were responsible for conducting the study design, data analysis and interpretation. All authors have read and approved the final manuscript.

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Not applicable.

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Tables

Table 1

Proportions used in decision model

	Point estimate	Range	References
Relapse of low risk group	0.15	0.10–0.20	Reference 6, 9, 12, 14, 15.
Relapse of high risk group	0.60	0.38–0.73	Reference 6, 9, 12, 14.
Progression after primary chemotherapy	0.05	0.01–0.10	Reference 12, 15–18.
Progression after salvage chemotherapy	0.05	0.01–0.22	Reference 6, 9, 14, 16, 18–20.
Progression after second-line chemotherapy	0		
Toxicity of Primary chemotherapy	1		
Toxicity of Salvage chemotherapy	3 × 1		
Toxicity of Second-line chemotherapy	3 × 1.3	3 × 1.0–3 × 2.0	Interview

Table 2 Results of survey for chemotherapy toxicity

No.	No chemotherapy	First-line chemotherapy		Second-line chemotherapy	
			Relative value		Relative value
1	95	85	0.895	75	0.789
2	95	75	0.789	50	0.526
3	80	70	0.875	65	0.813
4	95	70	0.737	50	0.526
5	95	70	0.737	50	0.526
6	90	70	0.778	50	0.556
7	95	80	0.842	50	0.526
8	100	80	0.8	60	0.6
9	90	85	0.944	60	0.667
10	95	80	0.842	65	0.684
11	90	80	0.889	60	0.667
12	90	70	0.778	50	0.556
13	90	80	0.889	70	0.778
14	85	58	0.682	37	0.435
15	100	90	0.9	87	0.87
16	100	100	1	96	0.96
17	100	99	0.99	93	0.93
18	95	70	0.737	45	0.474
19	100	80	0.8	50	0.5
20	85	70	0.824	50	0.588
21	95	75	0.789	50	0.526
22	90	80	0.889	40	0.444
23	95	85	0.895	60	0.632
24	90	80	0.889	60	0.667
Average			0.841		0.635
Standard deviation			0.081		0.151

Figures

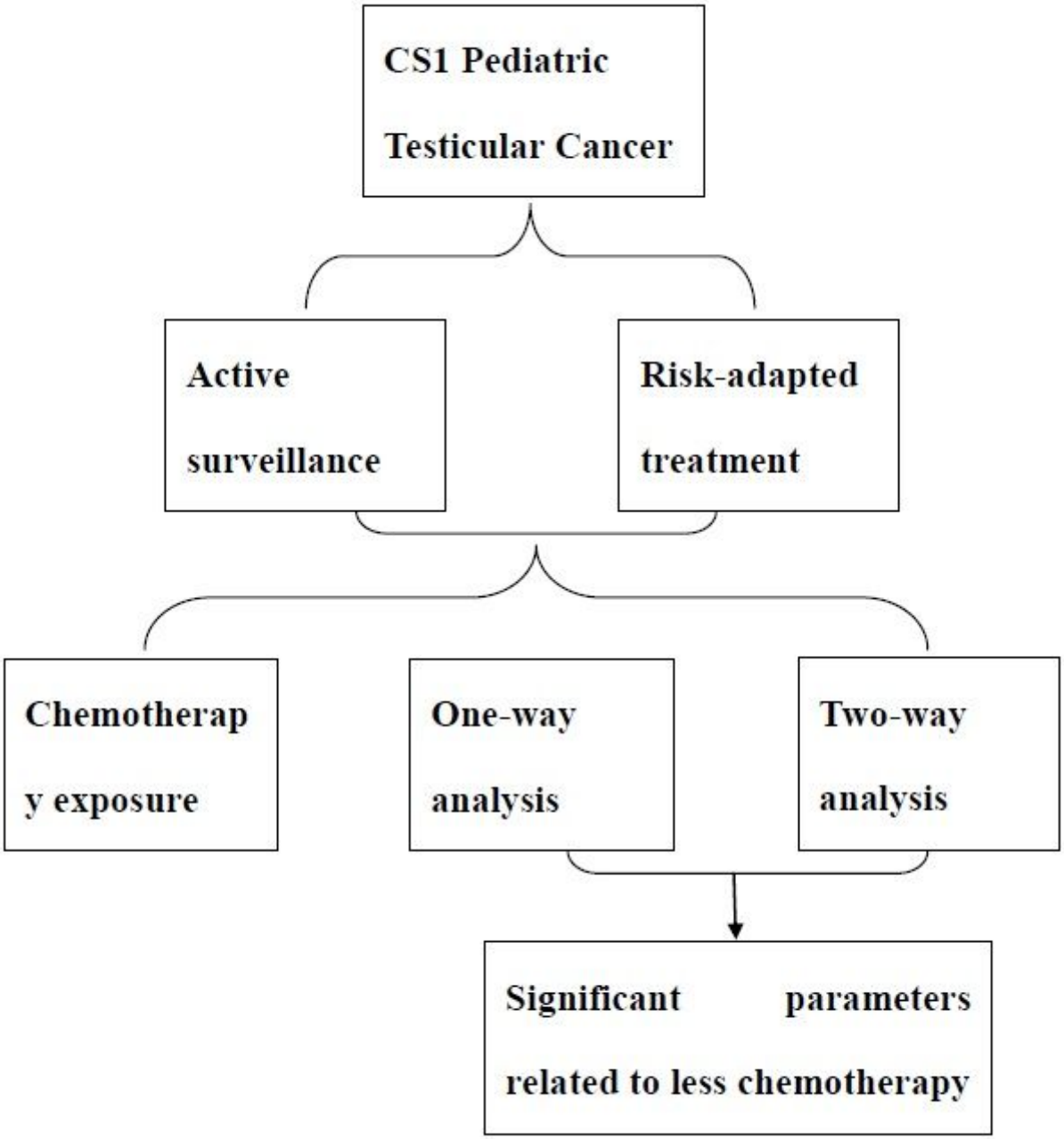

Figure 1

Flowchart of this decision analysis

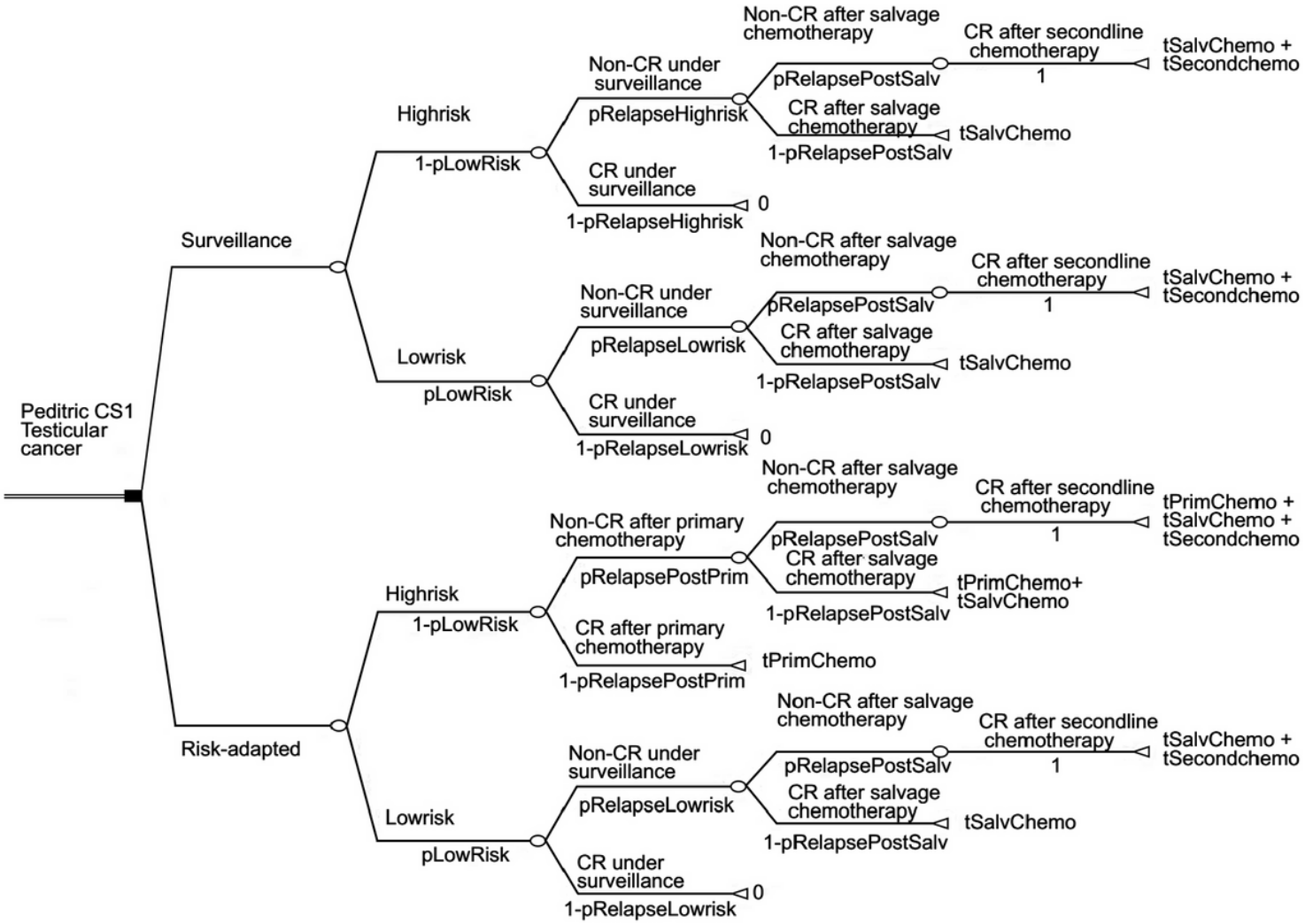

Figure 2

Decision analysis tree of risk-adapted treatment and surveillance

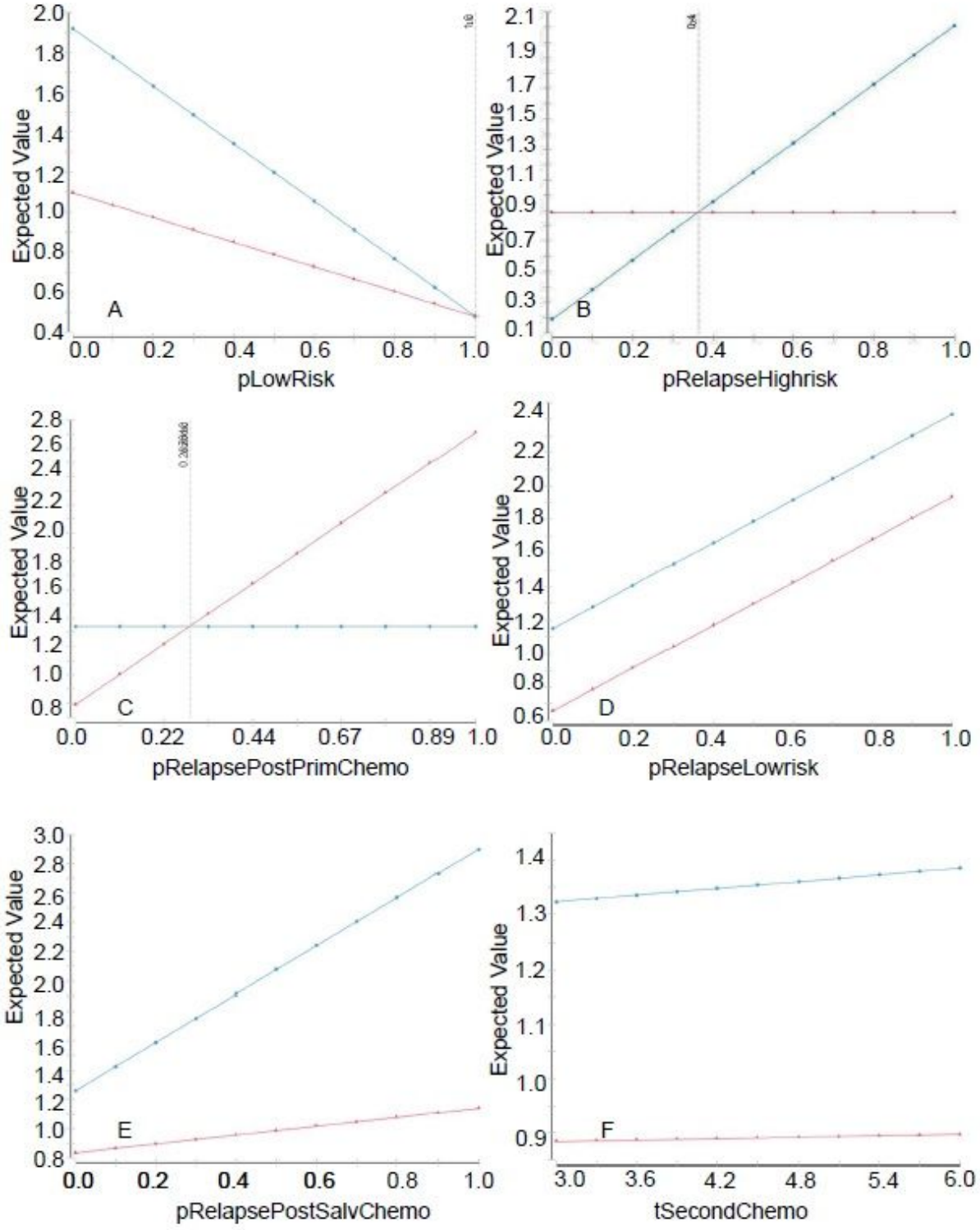

Figure 3

1-way sensitivity analysis A: In any value of pLowRisk (proportion of low-risk patients), surveillance was associated with higher exposure of chemotherapy; B: When pRelapseHighrisk (relapse rate of high-risk group) >0.365, surveillance was associated with higher exposure of chemotherapy; C: When pRelapsePostPrimChemo (relapse rate after primary chemotherapy) <0.287, surveillance was associated with higher exposure of chemotherapy; D: In any value of pRelapseLowrisk (relapse rate of low-risk

group), surveillance was associated with higher exposure of chemotherapy; E: In any value of pRelapsePostSalvChemo (relapse rate after salvage chemotherapy), surveillance was associated with higher exposure of chemotherapy; F: In any value of tSecondChemo (toxicity utility of second-line chemotherapy compared to salvage chemotherapy), surveillance was associated with higher exposure of chemotherapy. Red: risk-adapted treatment, Blue: surveillance

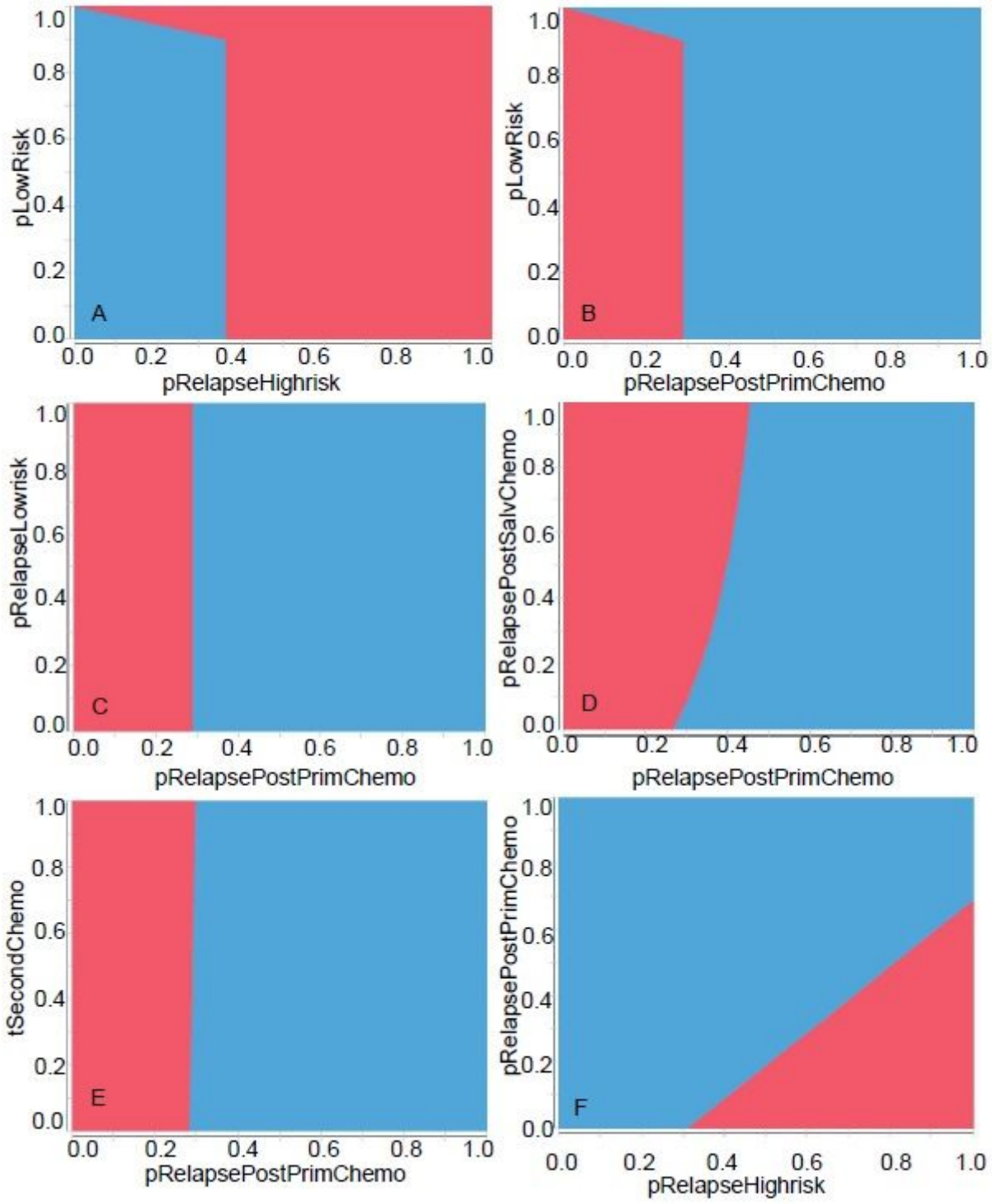

Figure 4

2-way sensitivity analysis A: In any value of pLowRisk (proportion of low-risk patients), when pRelapseHighrisk (relapse rate of high-risk group) >0.365, risk-adapted treatment was associated with lower exposure of chemotherapy; B: In any value of pLowRisk (proportion of low-risk patients), when pRelapsePostPrimChemo (relapse rate after primary chemotherapy) <0.287, risk-adapted treatment was associated with lower exposure of chemotherapy; C: In any value of pRelapseLowrisk (relapse rate of low-risk group), when pRelapsePostPrimChemo (relapse rate after primary chemotherapy) <0.287, risk-adapted treatment was associated with lower exposure of chemotherapy; D: In any value of pRelapsePostSalvChemo (relapse rate after salvage chemotherapy), when pRelapsePostPrimChemo (relapse rate after primary chemotherapy) <0.287, risk-adapted treatment was associated with lower exposure of chemotherapy; E: In any value of tSecondChemo (toxicity utility of second-line chemotherapy compared to salvage chemotherapy), when pRelapsePostPrimChemo (relapse rate after primary chemotherapy) <0.287, risk-adapted treatment was associated with lower exposure of chemotherapy; F: When pRelapsePostPrimChemo (relapse rate after primary chemotherapy) <0.1,and pRelapseHighrisk (relapse rate of high-risk group) >0.4, risk-adapted treatment was associated with lower exposure of chemotherapy. Red: risk-adapted treatment, Blue: surveillance

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFig1.1.pdf