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Postoperative chemotherapy on placental site trophoblastic tumor in early stage: analysis of 60 cases

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Summary

Purpose of Investigation: To review the literature of placental site trophoblastic tumor (PSTT) and explore the effect of postoperative chemotherapy in patients with Stage I. *Materials and Methods:* The authors searched literature on Medline, Excerpta Medica Database (EMBASE), and other resources using the keywords "placental site trophoblastic tumor" and "PSTT" from 1981 to 2014. *Results:* A total number of 60 patients with Stage I disease were identified, and the presentation, treatment, tumor response, disease status, and follow-up were retrieved and reviewed. According to the authors' knowledge, 725 cases associated with PSTT have been reported in 29 nations/areas since 1981. In this series, the probability of overall survival at ten years in the group of surgery alone and postoperative chemotherapy were 96.7% and 79.1% ($p = 0.199$), and recurrence-free survival rates were 91.8% and 63.3%, respectively. *Conclusion:* The benefit from postoperative chemotherapy is still equivocal. There is a need for scrupulousness before adding postoperative chemotherapy.

Key words: Placental site trophoblastic tumor; Gestational trophoblastic neoplasm; Gestational trophoblastic disease; Chemotherapy; Hysterectomy.

Introduction

Placental site trophoblastic tumor (PSTT) is the rarest variant of gestational trophoblastic diseases and originates from the implantation site intermediate trophoblast. PSTT typically occurs in reproductive-aged female patients. More than half of the patients with PSTT are diagnosed with Stage I disease and has a ten-year probability of overall survival of 90% [1]. However postoperative chemotherapy for early stage disease is still controversial. In this article the authors searched literature on Medline, Excerpta Medica Database (EMBASE), and other resources using the keywords "placental site trophoblastic tumor" and "PSTT" from 1981 to 2014. A total number of 60 patients with Stage I disease were identified, and the presentation, treatment, tumor response, disease status, and follow-up were retrieved and reviewed.

Materials and Methods

The authors searched literature on Medline, Excerpta Medica Database (EMBASE), and other resources using the key words "placental site trophoblastic tumor" and "PSTT" from 1981 to 2014. The nationality/area of author, published year, and number of cases of the articles or case reports associated with PSTT are summarized and shown in the world map (Figure 1). The presentation, treatment, tumor response, disease status, follow-up, and other information were reviewed and retrieved for 60 patients with Stage I disease. The probabilities of overall survival (OS) and recurrence-free survival were estimated by Kaplan-Meier analysis, and compared using the log-rank test. A two-tailed *p*-value of less than 0.05 was noted as statistically significant. Data were analyzed using SPSS version18 statistical software.

References for this Review were identified through searches of Medline, Excerpta Medica Database (EMBASE), and other resources with the search terms "placental site trophoblastic tumor", "PSTT", from 1981 to 2014. Both papers published in English and non-English languages were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Results

According to the present authors' knowledge, 725 cases associated with PSTT have been reported in 29 nations/areas since 1981. Of these, 226 (31.2%) cases were reported from USA, followed by China (151 [20.8%] cases), and the UK (134 [18.5%] cases) (Figure 1) [2-44, 45-87, 88-136]. In addition, a 35-year-old Somali woman with PSTT presenting with irregular bleeding and a mass in the lung was treated in USA, but was categorized as from Somalia [36].

In addition, 60 cases of PSTT with Stage I in literature were available and reviewed (Table 1). All these patients underwent hysterectomy with or without postoperative chemotherapy. In these patients, 21 underwent postoperative chemotherapy (Table 2), and 39 patients underwent surgery alone (Table 3). The proportion of patients who received hysterectomy in the surgery-alone group and post-

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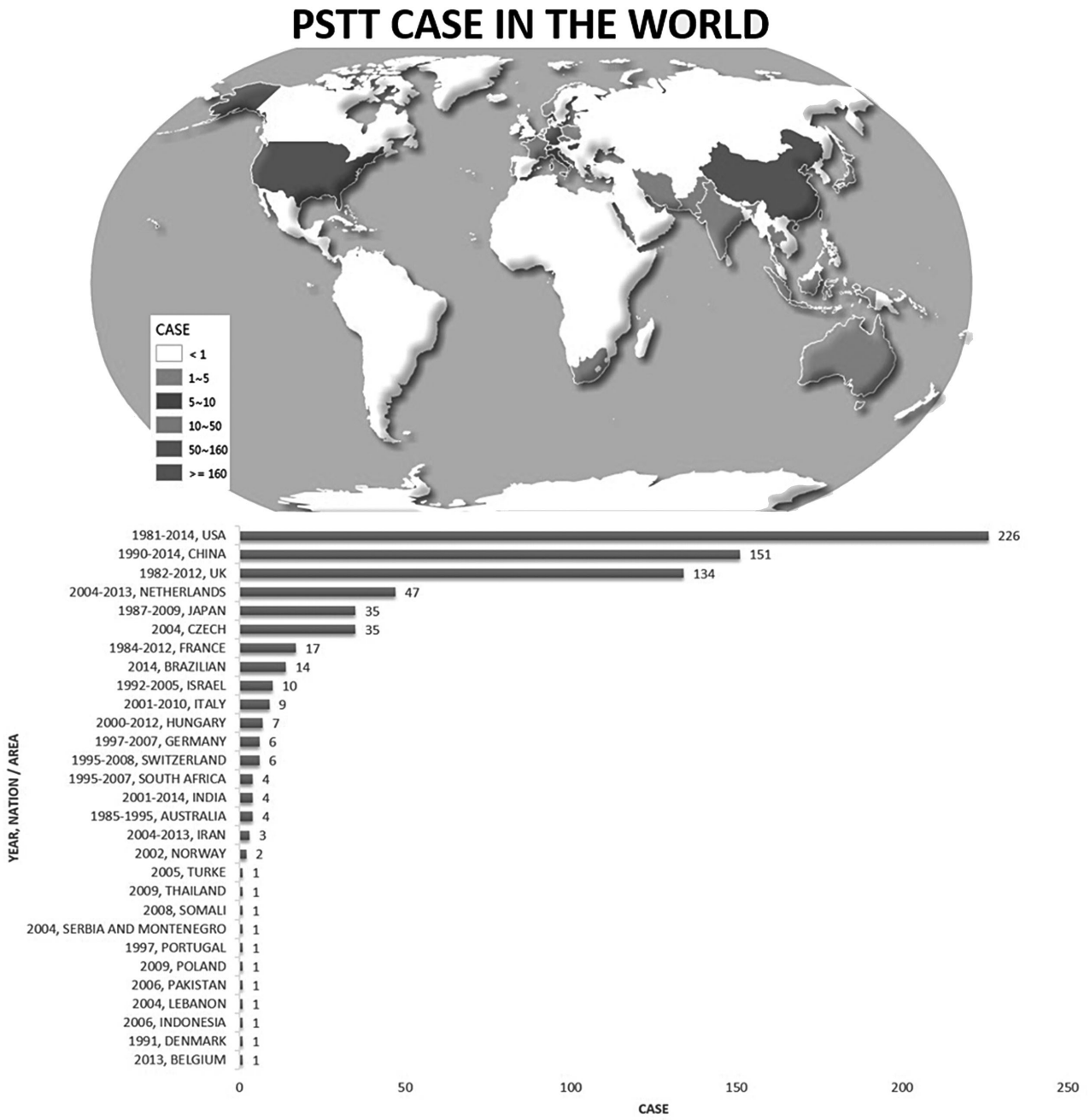

Figure 1. — To date, 725 of PSTT case have been reported in 29 nations/areas, since 1981.

operative chemotherapy group was 59.0% (23/39) and 52.3% (11/21), and was 35.9% (14/39) and 33.3% (7/21) with additional BSO/LSO/RSO (bilateral/left/right salpingo-oophorectomy), and was 10.2% (4/39) and 19.0% (4/21) with lymphadenectomy, separately. In the group of patients who underwent surgery alone and postoperative chemotherapy, the age was 30 years (median, range 20-62 years, 39 cases) and 35 years (median, range 18-53 years, 21 cases), interval from antecedent pregnancy (AP) was 12 months (median, range 3-84 months, 28 cases) and 12 months (median, range 1-131 months, 19 cases), hCG at diagnosis was 170.5 mIU/mL (median, range 18-4,500 mIU/mL, 25 cases) and 125 mIU/mL (median, range 5-8140 mIU/mL, 18 cases), mitoses/10 high-power fields

Table 1. — *The 60 patients with PSTT in literature*

	Postoperative chemotherapy	Surgery alone
Case (counts)	21	39
Age (years)	35 (median, range 18-53, 21 cases)	30 (median, range 20-62, 39 cases)
Presenting symptom		
IVB	38.1% (8/21)	15.3% (6/39)
Others (HA/Abd mass/AM/AO)	9.5% (2/21)	7.7% (3/39)
Interval from AP (months)	12 (median, range 1-131, 19 cases)	12 (median, range 3-84, 28 cases)
HCG at diagnosis	125 (median, range 5-8140, 18 cases)	170.5 (median, range 18-4500, 25 cases)
Dilation and curettage	53.2% (11/21)	76.9% (30/39)
Surgical treatment		
H	52.3% (11/21)	59.0% (23/39)
BSO/RSO/LSO	33.3% (7/21)	35.9% (14/39)
Lymphadenectomy	19.0% (4/21)	10.2% (4/39)
H+BSO/RSO/LSO+Lymphadenectomy	9.5% (2/21)	5·1% (2/39)
Mitoses/10HPF (counts)	6 (median, range 1-13, 12 cases)	4 (median, range 0-12, 34 cases)
Chemo	MTX/EMA-CO/EMA-EP/BEP	-
Follow-up(months)	38 (median, range 2-132, 20 cases)	46·8 (median, range 7-276, 37 cases)

Abd mass: abdomen mass; AM: amenorrhea; AO: abnormality of ovary; AP: antecedent pregnancy ; BSO: bilateral salpingo-oophorectomy; H: hysterectomy; HA: headache; IVB: irregular vaginal bleeding; LSO: left salpingo-oophorectomy; RSO: right salpingo-oophorectomy; MTX: methotrexate; EMA-CO: etoposide, methotrexate, and actinomycin-D (dactinomycin) alternating with cyclophosphamide and oncovin (vincristine); EMA-EP: etoposide and cisplatin alternating with etoposide, methotrexate, and actinomycin-D (dactinomycin); BEP: bleomycin, etoposide, cisplatin.

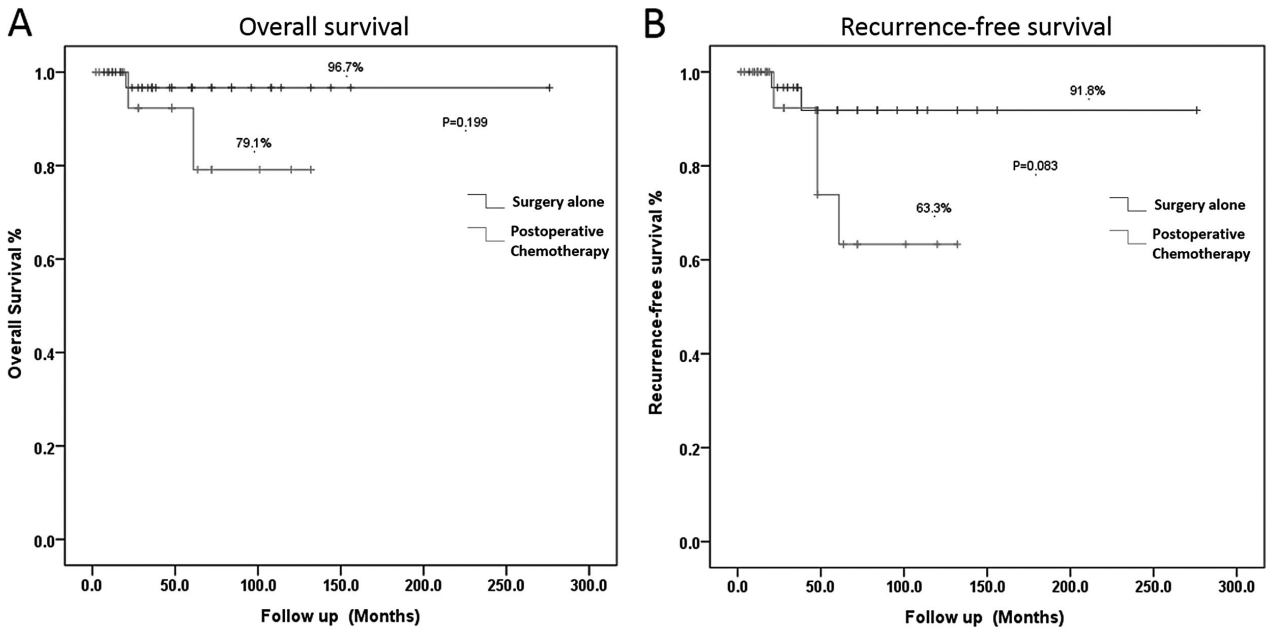

Figure 2. — A shows the overall survival at ten years. B shows the recurrence-free survival at ten years.

(HPF) was four counts (median, range 0-12 counts, 34 cases) and six counts (median, range 1-13 counts, 12 cases), and follow-up was 46.8 months (median, range 7-276 months, 37 cases) and 38 months (median, range 2-132 months, 20 cases), separately.

Discussion

PSTT is the rarest subtype of gestational trophoblastic neoplasm (GTN). PSTT can occur after any type of gestation. The duration from the preceding conception event is also highly variable. Most patients present with abnormal bleeding [93, 135, 137]. The optimized option for Stage I disease is hysterectomy with sampling of pelvic lymph nodes and ovarian conservation, unless the patient has a family history of ovarian cancer or is postmenopausal [138]. However, postoperative chemotherapy is still controversial.

Although there are limited data on patients with early

Table 2. — *The PSTTs treated with postoperative chemotherapy in literature.*

Author	Age (Year)	Gestation	PS	Interval from AP (months)	HCG (mIU/ml)	D & C	Treatment	Mitoses/10 HPF	Chemotherapy	Outcome	Follow-up **(months)**
Piura [44]	35	G7P4	IVB	5	540	+	H	3	EMA-CO	NED	132
Piura [44]	44	G4P2	IVB	9	164	+	H	6	EMA-EP	NED	12
Baergen [135]	35	G2P0		13	23	+	H/LSO	2	+	NED	72
Baergen [135]	21	G1P1		20	+	-	H/BSO	1	+	NED	63.6
Baergen [135]	43	G3P3		72	640	+	H	6	+	AWD	48
Baergen [135]	23	G2P1		72	696	+	H	1	+	NED	72
Baergen [135]	36	G4P2		88	33	-	H	2	+	NED	19.2
Baergen [135]	37	G5P2		131	8140	-	H/BSO/LR	13	+	DOD	21.6
Baergen [135]	39			>36	206	-	H	6	+	NED	27.6
Baergen [135]	53				10	+	H	7	+	AWD	48
Baergen [135]	30	G5P3			11000	+	H	10	+	NED	120
Gulati [136]	40				46		H /BSO/PLND		+		
Hoffman [131]	28			7	70		H/PLND	+/-	+	NED	12
Hyman [13]	18	G2	IVB	1	2346		H		MTX	NED	48
Hyman [13]	47	G4	IVB	2	99	+	H/VATS		MTX/EMA-CO /EMA-EP	NED	101
Hyman [13]	30	G2	HA/IVB	2	125	+	H		MTX	NED	2
Hyman [13]	33	G1	IVB	8	530	+	H		EMA-CO/EMA-EP	NED	9
Hyman [13]	43	G5	IVB	12			H/BSO		BEP	NED	28
Hyman [13]	38	G2	Abd mass /AM	65	5		H/BSO/VATS/Craniotomy		EMA-CO/EMA-EP /MTX	DOD	61
Machtinger [58]	33	G9P7	IVB	4.5	120-1200		H/LSO/PAL	12	EMA-CO/EMA-EP	NED	17
Saso [19]	27	G1P1		24	98	+	H/BPL		+	NED	4

Abd mass: abdomen mass; AM: amenorrhea; BPL: bilateral pelvic node lymphadenectomy; BSO: bilateral salpingo-oophorectomy; D & C:dilation and curettage; H:hysterectomy; IVB: irregular vaginal bleeding; LEILN: Left external iliac lymph node; LS: Lung Resection; LSO: left salpingo-oophorectomy; PAL: para-aortic lymphadenectomy; PALN: Para-aortic lymph node; PLN: pelvic lymph node; PLND: pelvic lymph node dissection; RSO: right salpingo-oophorectomy; VATS: video assisted thoracoscopic surgery; HA: headache; PS: Presenting symptom; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease; MTX: methotrexate; EMA-CO: etoposide, methotrexate, and actinomycin-D (dactinomycin) alternating with cyclophosphamide and oncovin (vincristine); EMA-EP: etoposide and cisplatin alternating with etoposide, methotrexate, and actinomycin-D (dactinomycin); BEP: bleomycin, etoposide, cisplatin.

Table 3. — *The PSTTs treated with surgery alone in literature*

Author	Age (Year)	Gestation	PS	Interval from AP (months)	hCG (mIU/ml)	D & C	Treatment	Mitoses /10HPF	Chemotherapy	Outcome	Follow-up (months)
Piura [44]	37	G5P4	IVB	5		+	H/BSO	8	-	NED	276
Baergen [135]	25	G1P1		6	18	+	H/RSO	3	-	NED	84
Baergen [135]	28	G1P1		6	+	+	H	3	-	NED	48
Baergen [135]	21	G1P0		7	1150	+	H/LSO	4	-	NED	24
Baergen [135]	21	G1P1		8		+	H	3	-	NED	144
Baergen [135]	31	G1P1		10	371	+	H/BSO	6	-	NED	114
Baergen [135]	28	G3P3		10	31	+	H/LSO	3	-	NED	60
Baergen [135]	36	G1P1		12	<5	+	H	6	-	AWD	38.4
Baergen [135]	26	G3P2		12	3000	+	H	7	-	NED	33.6
Baergen [135]	30	G1P0		12		+	H/BSO	4	-	NED	48
Baergen [135]	26	G2P2		16		-	H	6	-	NED	96
Baergen [135]	26	G2P2		17	659	+	H/LSO	5	-	NED	108
Baergen [135]	31			17		+	H	2	-	NED	84
Baergen [135]	37			17	160	+	H	1	-	NED	72
Baergen [135]	33	G1P1		18		-	H	1	-	NED	36
Baergen [135]	30			18		-	H	3	-	NED	16.8
Baergen [135]	28	G3P3		19		+	H	0	-	NED	60
Baergen [135]	20	G2P1		21	4500	+	H	4	-	NED	12
Baergen [135]	60	G4P4		60	+	+	H/BSO	5	-	NED	72
Baergen [135]	31	G2P2		84	42	+	H	4	-	NED	12
Baergen [135]	33			>72		+	H	1	-	NED	60
Baergen [135]	62	G3P3			181	-	H	4	-	DOD	20.4
Baergen [135]	32					+	H/BSO	1	-	NED	156
Baergen [135]	49				-	-	H/BSO/Radiatherapy	5	-	NED	132
Baergen [135]	-				25	-	H	3	-	NED	108
Baergen [135]	31					+	H	0	-	NED	84
Baergen [135]	20					+	H/BSO	4	-	NED	46.8
Baergen [135]	25	G2P2				+	H	2	-	NED	36
Baergen [135]	33	G4P2			1000	-	H	5	-	NED	36
Baergen [135]	26	G2P0			40-50	+	H	6	-	NED	30
Baergen [135]	29				186	+	H	4	-	NED	27.6
Chen [9]	41	G3P2	IVB	12		+	H		-	NED	30
Lan [27]	30	G4P1	IVB	3	32.7	+	H/LSO/PLND/OMNTC	12	-	NED	7
Lan [27]	26	G1P1	IVB	7	40.6	+	H	4	-	NED	18
Behnamfar [12]	26	G1P1	AM	36	101	+	H	2	-	NED	36
Hyman [13]	28	G1	IVB	15	<2	+	H/BSO		-	NED	14
Luiza [7]	53	G0P0	IVB		1517.7	+	H/BSO/BPL/PAL		-	NED	10
Saso [19]	31	G1P0	AO	12	20		H/PAL		-		
Saso [19]	37	G2P1	AM	24	265-385		H/PLND		-		

AM: amenorrhea; AO: abnormality of ovary; BPL: bilateral pelvic node lymphadenectomy; BSO: bilateral salpingo-oophorectomy; D & C: dilation and curettage; H: hysterectomy; IVB: irregular vaginal bleeding; LSO: left salpingo-oophorectomy; OMNTC: omentectomy; PAL: para-aortic lymphadenectomy; PLND: pelvic lymph node dissection; PS: Presenting symptom; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease.

stage PSTT, fertility-conserving therapy was reported in patients who showed a strong desire for future fertility and the pathological results showed no poor prognostic factors. Numnum *et al.* [47] reported a 29-year-old patient with early stage disease who received combination chemotherapy with etoposide, methotrexate, actinomycin-D followed by etoposide, and cisplatin (EMA-EP), and subsequently delivered a term infant two years after completion of therapy. Additionally, Shen *et al.* [18] reported six patients with early stage PSTT who were treated with chemotherapy and conservative surgery, and with a follow-up of ten to 104 months.

Chemotherapy was recommended in addition to surgery, considered for patients with Stage I disease who also have risk factors for recurrence, such as long interval from AP, vascular invasion, deep myometrial invasion, serosal involvement, lymphatic spread, high mitotic index, or persistently raised postoperative hCG [1, 27]. In the patients reported in literature, multi-agent regimen like EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) and EMA-EP (P-platinum) were the most available adjuvant chemotherapy, and BEP (bleomycin, etoposide, cisplatin) or MTX (methotrexate) was also successful [13, 44, 58, 135].

In this series, the probability of overall survival at ten years in the group of surgery alone and postoperative chemotherapy were 96.7% and 79.1% ($p = 0.199$) (Figure 2A), and recurrence-free survival rates were 91.8% and 63.3% ($p = 0.083$) (Figure 2B), respectively. In the group of surgery alone, one patient (1/37) died of disease in the follow-up of 20.4 months and one patient (1/37) was alive with disease in the follow-up of 38.4 months. However, in the postoperative chemotherapy group, two patients (2/20) died of disease in their follow-up of 21.6 and 61 months, and two patients were alive with disease in their follow-up of 48 months. Furthermore, the age of these six patients were more than the median of 30 or 35 years. Moreover, in the postoperative chemotherapy group, 3/4 patients with poor outcome were observed with more than 48 months of interval from AP, and more than five mitoses/10 HPF, which were considered risk factors of outcome.

It seems that the data of patients who underwent surgery alone showed a favorable result on overall survival and recurrence-free survival in patients with Stage I disease, although the *p*-values were statistically non-significant. Otherwise, PSTT were known to be chemoresistant, and the toxicity of chemotherapy would counteract the benefit for patient, which may contribute to the negative result of overall survival in the group of postoperative chemotherapy. It was indicated that scrupulousness is needed before adding postoperative chemotherapy or a more powerful multi-agent regimen on PSTT with Stage I disease, when patients were more than 30 or 35 years of age or other risk factors.

In this study, the authors failed to further perform a statistical analysis of risk factors due to the limitation of literature review and absence of data. Global, prospective, and random data is in sore need in future studies. However, postoperative observation is a considerable choice for patients with Stage I disease.

Conclusion

The oncologic outcome for patients who underwent surgery at ten years was comparable to patients with postoperative chemotherapy. The benefit from postoperative chemotherapy is still equivocal. There is a need for scrupulousness before adding postoperative chemotherapy or more powerful multi-agent regimen on Stage I PSTT. Postoperative observation is a considerable choice for patients with Stage I disease.

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