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Prognostic Factors for Outcome in Localized Extremity Rhabdomyosarcoma. Pooled Analysis From Four International Cooperative Groups

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Abstract

Background—Extremity rhabdomyosarcomas do not always show satisfactory outcomes. We analyzed data from 643 patients treated in 14 studies conducted by European and North American groups between 1983 and 2004 to identify factors predictive of outcome.

Procedure—Clinical factors, including age; histology; site of primary (hand and foot vs. other); size; invasiveness (T stage); nodal involvement (N stage); and treatment factors, including post-surgical group; chemotherapy type and duration; radiotherapy; and treatment (before or after 1995); were evaluated for impact on overall survival (OS).

Results—5-year OS were 67% (se 1.8). Multivariate analysis showed that lower OS correlated with age >3 years, T2 and N1 stage, incomplete initial surgery, treatment before 1995, and

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European cooperative group treatment. Patients with gross residual disease after initial incomplete resection/biopsy had similar outcomes in both continental groups. The better global survival of patients treated in American studies was accounted for by differences in outcome in the subset of those with grossly resected tumors (OS 86% [se 3] for COG patients vs. 68% [se 4] for European patients ($P = 0.004$)). When excluding chemotherapy duration from the model, analysis in this subset of patients showed that cooperative group ($P = 0.001$), site ($P = 0.001$), and T stage ($P = 0.05$) were all significant. However, after adding duration of chemotherapy (≥ 27 weeks) to the model, only primary site remained significant ($P = 0.006$).

Conclusion—This meta-analysis confirms the role of many established prognostic factors but identifies for the first time that chemotherapy duration may have an impact on outcome in patients with grossly resected tumors.

Keywords

extremity; pediatric; prognosis; rhabdomyosarcoma

INTRODUCTION

Rhabdomyosarcoma (RMS) arises in a multiplicity of sites, and primary location in the extremities accounts for approximately 15% of localized RMS. Sequential clinical studies by international collaborative groups have failed to improve the outcome for children with extremity RMS, which remains suboptimal compared with that of children with RMS at more favorable sites.[1–5] Several adverse factors are frequently associated with extremity RMS, including older age, alveolar subtype (ARMS), and nodal involvement.[5–7]

We describe the results of collaboration between four cooperative study groups in Europe and North America to evaluate prognostic factors for extremity RMS and offer data on the largest number of prospectively treated extremity RMS patients reported to date.

MATERIALS AND METHODS

Data were collected from the files of the Intergroup Rhabdomyosarcoma Study (IRS) Group, now the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG), in North America; and the Cooperative Weichteilsarkom Studiengruppe (CWS), Italian Cooperative Group for Pediatric Soft Tissue Sarcomas (ICG) and the International Society of Paediatric Oncology Malignant Mesenchymal Tumour Committee (SIOP) in Europe.

Extremity site was defined as any part of the upper and lower extremity, buttock, and shoulder girdle. Data were collected from 643 patients, diagnosed between 1983 and 2004, treated within the following protocols: IRS/COG: IRS-III, IRS-IVP, IRS-IV, D9803 (n = 300 patients);[2,8–10] ICG RMS-79, −88, −96 (n = 44);[1] CWS-81, −86, −91, −96 (n = 139); [3,11,12] and SIOP MMT-84, −89, −95 (n = 160).[4,5,13]

All complied with the Helsinki Declaration regarding human experimentation. Informed consent was obtained in line with research ethics requirements at each participating institution. Completeness of initial surgical resection is reported using the IRS Clinical Grouping system (Supplemental Table I).

All of these protocols utilized similar chemotherapy regimens, with either VA (vincristine, actinomycin D), VAC (vincristine, actinomycin D, cyclophosphamide), IVA (ifosfamide + VA), VAIA (adriamycin + IVA), EVAIA (etoposide + VAiA), VACA (VAC + adriamycin), or CEVAIE (carboplatin, epirubicin + EVAIA) at approximately equivalent myelotoxic doses. Some patients on COG D9803 also received topotecan (Supplemental Table II).

Duration of the chemotherapy varied between groups: duration of European chemotherapy protocols was 24–27 weeks, compared with 46 weeks for the chemotherapy regimens used by the COG protocols (Supplemental Figure 1).

Radiotherapy (RT) requirements also varied between treatment groups. COG protocols recommended systematic local therapy including radiation therapy for all patients except those with primary completely resected embryonal RMS (ERMS). SIOP and ICG protocols limited the indication for systematic use of RT to patients who did not achieve complete remission with chemotherapy with/without secondary surgery. In the CWS studies, radiation dose was stratified depending on the results of second-look surgery. Only patients who did not undergo second-look surgery or who had a residue were irradiated (Supplementary Data 1).

Statistical Methods

Intergroup consensus determined the data items for analysis (Supplemental Table III). Data were pooled in a master database at Gustave Roussy where analyses were performed.

Progression free survival (PFS) was defined as the time from the start of treatment to disease progression/relapse or death from any cause. Overall survival (OS) was defined as the time from the start of treatment to death from any cause. The Kaplan–Meier method was used to estimate the PFS and OS distributions. Differences between survival curves were analyzed by the log-rank test. The distributions of categorical participant characteristics were compared between the groups using χ^2 or Fisher's exact tests. Multivariate comparisons of time to event distributions were made using the Cox proportional hazards model.

RESULTS

The characteristics of patients and tumors are described in Table I.

Patient Demographics and Tumor Characteristics

Median age at diagnosis was 6.3 years (0–20.8). Nearly one-third (29%) of the patients were <3 years of age and one-third (35%) were >10 years. Based on morphology, 420 patients (65%) had alveolar RMS, with a similar proportion in each cooperative group. However, diagnostic definition of alveolar subtype ARMS has evolved with time and tumors diagnosed before 1995 were significantly less often identified as alveolar than tumors diagnosed later on (61% vs. 70%, $P < 0.03$).

Primary sites were located in lower limbs in 58% patients and in upper limbs in 41% (not specified in one); 49% were located proximally and 51% distally. Overall 17% patients had

primaries in the hand (n = 55) or foot (n = 53). Tumor characteristics according to cooperative groups are described in Supplemental Table IV.

Clinical, radiological, or pathological evidence of proximal nodal involvement of proximal lymph nodes was detected recorded in 21% patients and was significantly more frequent in patients with ARMS (26.3% vs. 10.6% in ERMS, $P < 0.02$). Histologically proven involvement was also more frequent for ARMS than ERMS (40% vs. 16%, $P < 0.001$).

Lymph node sampling was recommended but not required in all studies and only required on COG D9803. Differences in recommended/required investigations may account for variations in rates of nodal involvement identified between groups, ranging from 24% (COG) to 14% (SIOP).

Initial Surgery

All patients had at least a biopsy and 58% underwent an initial attempt at surgical resection, although this varied between the groups from 63% (COG) to 43% (ICG) ($P = 0.001$). Initial complete excision was achieved in 23% (IRS Group I) whereas 24% had microscopic positive margins (Group II) and 53% had macroscopic residue after resection or were only biopsied (Group III). Completeness of surgery was more often achieved in COG patients (30%) compared to other groups (range: 13–23%) ($P < 0.002$). Amputation was performed as a primary procedure in 28 (9%) COG patients; this included 11 with digit/ray amputations in hands/feet (Supplemental Table V).

Chemotherapy

All patients received multiagent chemotherapy in various combinations according to groups and treatment eras (Supplemental Table II).

Radiation Therapy

Overall, 376 (59%) patients received RT as part of primary treatment. This varied significantly between groups: only 29% were irradiated in SIOP studies compared to 67% (IRS/COG), 73% (CWS), and 73% (ICG).

Patients who received RT were older and there was further variation in the delivery of RT to very young (<3years) patients (IRS/COG, 25%; CWS, 13%; ICG, 19%; SIOP, 13%) (Supplemental Table VI).

Radiation doses ranged from 16.2 to 66 Grays (median 45 Grays). Radiation was delivered only to the primary in 84% and to primary site with regional nodes in 16% (field data were available for 72% of irradiated patients).

Remission, Survival, and Relapse

Median follow-up of survivors was 8.2 years (1.9–22 years). Five- and ten-year OS rates were 67% (standard error (SE) 1.8) and 62% (SE 2), respectively.

Twenty-four (3.7%) patients progressed and died without achieving tumor control and 258 (40%) relapsed. Median time to relapse was 17 months, only 3% occurring ≥5 years from diagnosis. Five- and ten-year PFS rates were 54% (se 1.9) and 51% (se 2.0), respectively.

Loco-regional failure occurred in 163 patients (63% of all relapses), with simultaneous metastasis in 41. Site of failure (details specified in 118 patients) was primary site in 57%, regional lymph nodes in 33%, and both primary and nodal sites in 10%. Local failure occurred more often in patients who did not receive initial irradiation (31% vs. 22% in those receiving RT as part of primary treatment, $P = 0.02$). Radiation dose had no impact on the risk of locoregional relapse. Metastatic relapse was documented in 95 patients (37% of all relapses). Histological subtype was not associated with the pattern of relapse (Supplemental Table VII). Ten patients developed a second tumor as first event.

Overall, 91% (230/252) of all deaths were attributed to the primary disease; 10 died from treatment toxicity, six from second malignancy, and four from other, unrelated causes. The cause of death was unknown for two patients.

Survival after relapse was very poor: 5-year survival was only 32% after isolated local relapse, 12% after metastatic relapse, and 9% after combined relapse. Survival after relapse was significantly better for patients who did not receive RT as part of the initial treatment (33% vs. 16% for patients who had received RT, $P < 0.001$).

Details of treatment for relapse were not available to allow analysis of overall burden of therapy, but within the COG studies; 76% of the surviving patients had received radiation therapy or had undergone amputation during initial treatment of the primary disease. Among the European groups, the use of RT and/or amputation varied widely from 24% in surviving SIOP patients to 79% in CWS and 81% in ICG patients.

Prognostic Factors

Analysis on the whole population—Table I shows OS by prognostic variable. Survival differed by age: age 3 years or more being associated with a less favorable outcome ($P < 0.001$). Patients less than 1 year had the same survival as patients 1–3 years old. The risk for patients 3–9 years old appeared to be intermediate to that of patients between 0 and 3 years old and those who were ≥10 years or older ($P = 0.02$). (Supplemental Figures 2A and B).

Tumor invasiveness (T2 stage ($P < 0.001$), large tumor size ($P = 0.002$), lymph node involvement ($P < 0.001$), and incomplete initial surgery ($P < 0.001$)) were all strongly correlated with lower survival. Pathological subtype had only a borderline impact on OS ($P = 0.06$) and tumors of hand and foot ($P = 0.08$) tended to do worse than other sites. RT as part of the initial treatment did not correlate with OS. Period of treatment had an impact, with patients treated more recently doing better. Overall survival was identical in the European cooperative groups (62% at 5 years) but significantly lower than that seen in the IRS/COG studies ($P = 0.002$).

Multivariate analysis on 592 patients with complete data (Table II) demonstrated that age ($P = 0.002$), T status ($P = 0.02$), nodal involvement ($P = 0.04$), completeness of initial surgery

($P = 0.001$), and era of treatment ($P = 0.001$) were independently predictive of OS. Cooperative group maintained an independent prognostic impact ($P = 0.001$).

Further analysis of=this difference showed that the outcome was different only for patients with grossly resected tumors after initial surgery (IRS Groups I and II). The outcome of IRS Group III patients (macroscopic residual/biopsy alone) was identical for all groups (Fig. 1A and B).

Analysis for patients with grossly resected primaries (IRS Groups I and II) without nodal involvement—In this subset of 252 patients, univariate analysis (Table III) showed that, in addition to the influence of cooperative group ($P = 0.0004$), completeness of initial surgery ($P = 0.05$), T status ($P = 0.02$), and primary site (hand/foot vs. other extremity sites, $P = 0.01$) all correlated with OS. Furthermore, the duration of chemotherapy was strongly associated with OS ($P = 0.002$), with lower local and metastatic relapse rates in those treated 27 weeks or more. Histology, age at diagnosis, size of the tumor, radiation therapy as part of the initial treatment, and treatment period had no impact.

In multivariate analysis only tumor site ($P = 0.006$) and duration of chemotherapy ($P < 0.001$) were independently predictive of OS (Table IV). The strong association between cooperative group and duration of chemotherapy (IRS/COG trials uniformly using longer duration of therapy) did not allow further analysis.

DISCUSSION

The results of this analysis of a large international cohort of patients show that extremity RMS in patients without distant metastatic disease occurs at a median age (6.3 years) similar to parameningeal or orbital tumors[14,15] but older than in other sites such as bladder/prostate (2.5 years).[16]

The 10-year OS rate of 62% confirms the relatively less favorable prognosis of extremity RMS as compared to other sites. [2,3,5,12] Age is a prognostic factor and patients ≥10 years old or more had a poorer survival than younger patients, consistent with data from other studies.[14,17–19] However, patients less than 3 years had a better survival than patients between 3- and 9-years-old despite the challenges of delivering local therapy to very young children. Other adverse prognostic factors measurable at diagnosis included, tumor invasiveness (T2 stage), tumor size (>5 cm), and locoregional nodal involvement, findings similar to those reported for RMS regardless of tumor site.[4,6,14,20]

Nodal involvement was common (21%) and more common for alveolar than for non-alveolar tumors. This is in line with data in a detailed study of patterns of nodal involvement in extremity RMS which also raised the issue of managing potential/confirmed involvement of in-transit nodes.[21] In that study, patients who underwent complete lymph node staging with appropriate radiotherapy to the in-transit nodal site were at slightly lower risk of in-transit failure. However, the delivery of optimal local therapy to limit failure in in-transit nodes in patients with extremity tumors remains a challenge.[22] Assessment using sentinel lymph node sampling and FDG-PET scanning may help refine the diagnosis of lymph node

involvement at diagnosis but the place of such technologies is not yet fully established in the management of RMS.[23–25]

ARMS is frequent in extremity sites and was found in 65% of the tumors, a proportion similar across all the groups despite long-standing discussions about its definition.[26] Although alveolar subtype has been identified as a poor prognostic factor in many studies[2,4,6,9,15,16,27] it did not correlate with a worse outcome in this series, either in univariate or multivariate analysis, nor was it associated with a specific pattern of failure. This possibly reflects increased treatment intensity and routine use of radiation for ARMS.

However, similar findings emerged from an analysis of metastatic RMS[19] reflecting the fact that ARMS not only occurs more often in extremity sites but is also more often metastatic at diagnosis than ERMS, but is not per se an independent prognostic factor. The new definition based on molecular biology and currently used in RMS protocols might impact the prognostic value of RMS alveolar subtype in future studies.[28]

Overall, patients treated in North American studies fared better than patients treated in Europe, even after adjustment for other prognostic factors. This was accounted for by differences in outcome for grossly resected (IRS Group I–II) tumors without node involvement. In this subset of patients, multivariate analysis showed that tumor invasiveness and location in hands/feet were prognostically important in addition to cooperative group. There was no effect from the use of RT during initial treatment and although the difference seen in outcome might reflect differences in initial surgical approach, an unexpected finding was attributable to the difference in duration of chemotherapy and its independent impact on survival. Treatment duration was 27 weeks or longer in all COG patients but shorter than 27 weeks in 90% of the European patients. The impact of treatment duration has not been previously reported as prognostic in studies of RMS, but the value of prolonged additional treatment with “maintenance” chemotherapy is now under exploration in current European studies.

As with all meta-analyses, the interpretation of our results comes with inherent limitations. For example, there was significant evolution in imaging modalities that could influence stage, changes in the histological definition of ARMS, and refinements in radiation therapy technologies during the review period. Comparisons between patients enrolled on differing protocols are non-randomized and uncontrolled. Nonetheless, our large study size and common elements of data collection allow us to make comparison that would not be possible within a single, smaller clinical study.

CONCLUSIONS

The value of pooled analysis of data from parallel international studies of RMS has been demonstrated in several previous reports. [14–16,19,28–30] Optimizing therapy for children with RMS at extremity sites remains a challenge for all studies. Data from this analysis, and from other current literature, suggest that efforts should be focused on: better recognition of lymph node status at diagnosis and improving methods for treating those with nodal involvement, including the management of in-transit nodes; improving primary surgical

resection, whilst retaining limb function; and optimizing chemotherapy, targeting in particular better treatment for ARMS and the place of longer duration of therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ARMS	alveolar rhabdomyosarcoma
COG	Children's Oncology Group
CWS	Cooperative Weichteilsarkom Studiengruppe
ERMS	embryonal rhabdomyosarcoma
ICG	Italian Cooperative Group
IRS	Intergroup Rhabdomyosarcoma Study
MMT	malignant mesenchymal tumors
N ?stage	nodal involvment
OS	overall survival
PFS	progression free survival
RMS	rhabdomyosarcoma
RT	radiotherapy
SIOP	International Society of Paediatric Oncology
T stage	invasiveness

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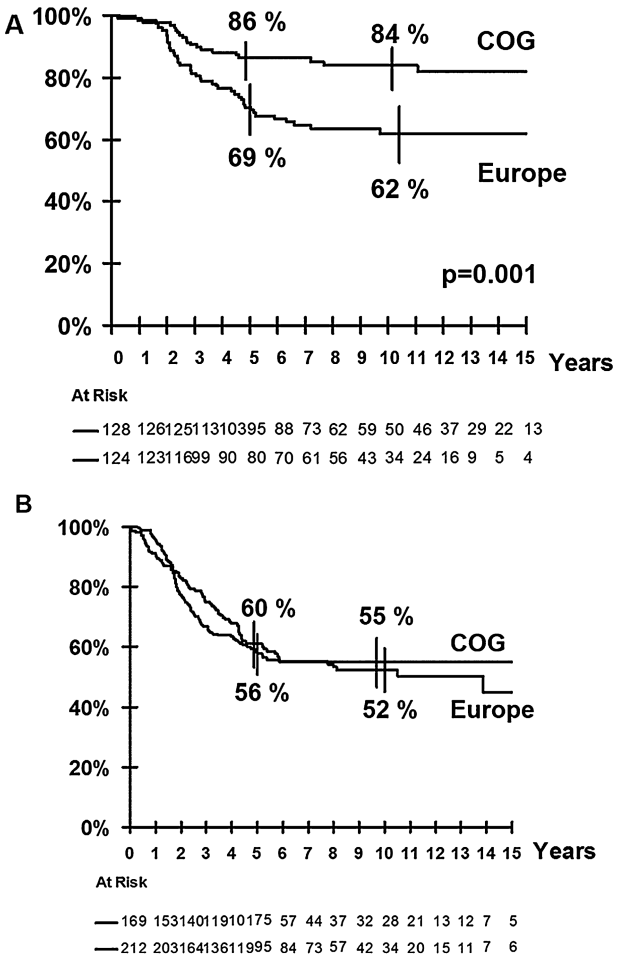

Fig. 1.

Overall survival by continental groups. (**A**) Overall survival for grossly resected tumors: complete surgery (IRS group 1) or microscopic residue (IRS group 2). (**B**) Overall survivals for unresected tumors or resected tumor with macroscopic residue (IRS group 3).

TABLE I

Characteristics of the 643 Patients and Overall Survival Rates by Prognostic Variables

Variables	No	5-year OS (%)	10-year OS (%)	RR of death	Log-rank test (*P*)
Total	643	67	62		
Sex					
Male	327	66	62	1.1	NS
Female	316	69	62	1	
Age					
<3	189	79	71	1	
3–9	232	65	61	1.6	0.03
10+	222	59	54	1.9	
Age					
<3	189	79	71	1	<0.001
3+	454	62	58	1.7	
Site of primary					
Upper limb	264	66	61		
Lower limb	373	68	62		NS
Site of primary					
Hand and foot	108	57	55	1.3	
Other	529	69	63	1	0.08
T status					
T1	398	75	70	1	
T2	222	54	49	2.1	<0.001
Unknown	23				
Tumor size					
<5 cm	270	75	70	1	
>5 cm	364	62	56	1.7	0.002
Unknown	9				
Clinical stage					
I	346	78	71	1	
II	133	58	53	2.1	<0.001
III	131	51	46	2.5	
Unknown	33				
Regional node involvement					
No	495	72	66	1	<0.001
Yes	131	51	46	1.9	
Unknown	17				
Pathology					
Non alveolar	223	72	68	1	0.06
Alveolar	420	65	58	1.4	
Initial surgery					
Complete	148	82	77	1	

Variables	No	5-year OS (%)	10-year OS (%)	RR of death	Log-rank test (*P*)
Micro residue	153	71	66	1.6	<0.001
Macro residue or biopsy	101+239	59	52	2.8	
Chemotherapy					
VA	39	84	81	1	
Alkyating agents (AA)	307	69	64	2	0.04
AA + any anthracyclines	197	64	57	2.4	
6 drugs (CEVAIA)	94	57	55	2.7	
Unknown	6				
Initial radiation					
No	231	68	64	1	
Yes	388	66	59	1.1	NS
Unknown or amputation	24				
Cooperative groups					
COG	300	72	68	1	
CWS	139	63	54	1.5	0.02
ICG	44	64	59	1.5	
SIOP	160	61	56	1.5	
Cooperative groups					
COG	300	72	68	1	0.002
Europe	343	62	56	1.5	
Era of treatment					
1984–1994	355	62	57	1.5	0.004
1995+	288	73	68	1	

NS, not statistically significant.

TABLE II

Cox Model for Overall Survival (n = 592 Patients With Complete Data)

Prognostic variables	Relative risk of death	*P*
Age (years)		
<3	1	
3+	1.7 (1.2–2.4)	0.002
T status		
T1	1	
T2	1.4 (1.1–2)	0.02
Tumor size		
<5cm		NS
>5cm		
Site of the Primary Tumour		
Hand and foot		NS
Other		
Lymph Node involvement	1	
No	1.4 (1–1.9)	0.04
Yes		
Initial surgery		
Complete	1	
Micro residue	1.5 (0.9–2.3)	
Macro residue	2.3 (1.5–3.6)	0.001
Initial radiation		
No		
Yes		NS
Cooperative groups		
COG	1	
Europe	1.6 (1.2–2.2)	0.001
Era of treatment		
1984–1994	1.7 (1.3–2.3)	
1995+	1	0.001

TABLE III

Overall Survival Rates by Prognostic Variables for Grossly Resected Tumors Without Nodes

Variables	No	5 year OS (%)	RR of death	Log-rank test (*P*)
Total	252	78 (73–83)		
Age				
<3	72	86 (76–92)	1	NS
3+	180	75 (69–81)	1.51	−0.17
Site of the primary tumour				
Upper limb	112	75 (66–82)	1.34	NS
Lower limb	136	81 (74–87)	1	−0.25
Site of the primary tumour				
Hand and foot	43	64 (48–77)	2.09	0.01
Other	205	82 (75–86)	1	
T status				
T1	203	82 (76–86)	1	0.02
T2	43	67 (52–79)	1.92	
Unknown	6			
Tumor size				
<5 cm	151	80 (72–85)	1	NS
>5 cm	96	77 (67–84)	1.29	−0.32
Unknown	5			
Pathology				
Non alveolar	90	83 (74–89)	1	NS
Alveolar	162	76 (69–82)	1.47	−0.16
Initial surgery				
Complete (IRS I)	136	83 (76–88)	1	0.05
Micro residue (IRS II)	116	73 (64–23)	1.65	
Chemotherapy				
VA	36	86 (71–94)	1	NS
Alkyating agents (AA)	103	85 (77–91)	1.02	−0.07
AA + any anthracyclines	94	70 (60–79)	1.98	
6 drugs (CEVAIA)	18	66 (43–84)	2.04	
Unknown	1			
Chemotherapy duration				
< 23 weeks	52	70 (56–81)	2.39	0.004
24–26 weeks	59	69 (56–79)	2.39	
>27 weeks	141	85 (79–90)	1	
Initial radiation				
No	104	79 (70–85)	1	NS
Yes	129	77 (69–84)	0.99	
Unknown or amputation	19			
Amputation				

Variables	No	5 year OS (%)	RR of death	Log-rank test (*P*)
No	234	78 (72–83)	0.86	NS
Yes	18	83 (59–94)	1	
Cooperative groups				
COG	128	86 (79–90)	1	0.004
Europe	124	70 (62–78)	2.51	
Era of treatment				NS
1984–1994	171	76 (69–82)	0.91	−0.1
1995+	81	83 (74–90)	1	

TABLE IV

Cox Model for Overall Survival for Grossly Resected Tumors Without Nodes, IRS I and II (n = 252)

	Model without chemotherapy duration		Model including chemotherapy duration	
Prognostic variables	**Relative risk of death**	***P***	**Relative risk of death**	***P***
Initial surgery				
Complete				
Micro residue		NS		
Site of the PT				
Hand and foot	2.2	0.01	2.2	0.006
Others	1		1	
T status				
T1	1			
T2	1.8	0.05		NS
Cooperative groups				
COG	1			
Europe	2.6	0.001		NS
Duration of chemotherapy				
<27 weeks			2.6	
>27 weeks			1	<0.001