Supplemental Online Content

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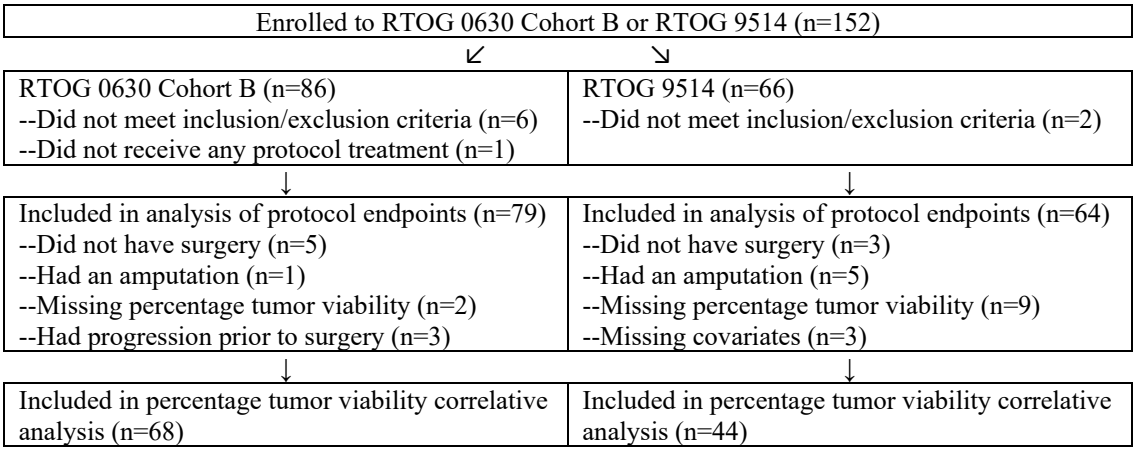
This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flow Diagram



eAppendix. Report

Statistical Methodology

For the RTOG 0630 long-term update and ancillary project, rates of local, regional, and distant failure and second primary tumor were estimated by the cumulative incidence method, to account for the competing risk of death without failure. Rates of distant disease-free, disease-free, and overall survival (OS) were estimated by the Kaplan-Meier method. All event times were measured from the date of registration to RTOG 0630 to the date of event, competing event, or last follow-up. To allow comparison with the results of the CAN-NCIC-SR2 trial preoperative arm, the event-free proportions were estimated by the Kaplan-Meier method for local recurrence, regional/distant recurrence, and progression-free survival, after excluding patients that did not have surgery and those that had an amputation. For the ancillary project, Kappa statistics were calculated to evaluate the agreement of local and central review of histologic type, histologic grade, and R status; patients with unknown/unclassified values were excluded. For this part of the analysis only, survival and disease outcomes were recalculated from the date of surgery; patients that did not have surgery, had an amputation, or had progression prior to surgery were excluded. Hazard ratios were estimated by the Cox model, stratified by study. The final multivariable model was selected by minimizing Akaike Information Criterion (AIC). Alternative models with (1) AIC within 2 units of the smallest AIC for all candidate models and (2) replacing liposarcoma with myxoid/round cell liposarcoma (or vice versa) are also presented to evaluate the robustness of the post-treatment tumor viability effect on outcomes. Only patients with complete data for all potential covariates (age, gender, race, Zubrod performance status, disease location, disease size, histologic grade, time to surgery, R status, histologic type, and percentage tumor viability) were included in the analysis. When hazard ratios could not be estimated, the stratified log-rank test was used to assess differences in outcomes by tumor viability; for univariate analysis, the test was stratified by trial; and for multivariable, by trial and other variables in the model. Where central review data were available, they were used (100% for percentage tumor viability; 94% for histologic grade; 94% for histologic type; and 99% for R status); otherwise, local data were used.

eTable 1. Late Toxicities of Interest at 1-5 Years in RTOG 0630

Toxicity	Toxicity/Total	Toxicity (%)	95% CI (%)
Grade 2+ subcutaneous tissue fibrosis [1], joint stiffness [1], or edema [2]			
1 year	8/63	12.7	4.5, 20.9
2 years	6/57	10.5	2.6, 18.5
3 years	3/46	6.5	0.0, 13.7
4 years	3/39	7.7	0.0, 16.1
5 years	2/24	8.3	0.0, 19.4
Grade 2+ subcutaneous tissue fibrosis [1]			
1 year	1/64	1.6	0.0, 4.6
2 years	3/56	5.4	0.0, 11.3
3 years	0/46	0.0	-
4 years	2/40	5.0	0.0, 11.8
5 years	1/24	4.2	0.0, 12.2
Grade 2+ joint stiffness [1]			
1 year	5/63	7.9	1.3, 14.6
2 years	2/56	3.6	0.0, 8.4
3 years	1/46	2.2	0.0, 6.4
4 years	2/40	5.0	0.0, 11.8
5 years	1/24	4.2	0.0, 12.2
Grade 2+ edema [2]			
1 year	3/66	4.5	0.0, 9.6
2 years	3/58	5.2	0.0, 10.9
3 years	2/46	4.3	0.0, 10.2
4 years	2/39	5.1	0.0, 12.1
5 years	1/24	4.2	0.0, 12.2

CI, confidence interval.

[1] RTOG/EORTC criteria.

[2] Stern's scale.

All time points are measured from the start of radiation therapy and include a window of +/- 3 months.

eTable 2. Treatment-Related Late Adverse Events Ocurring in At Least 5% of Patients in RTOG 0630 (n=75)

	Grade					
Adverse Event	1	2	3	4	Grade 1-4 (%)	Grade 2-4 (%)
Any	28	28	10	1	89.3	52.0
Edema limbs	27	11	3	0	54.7	18.7
Skin induration	22	7	1	0	40.0	10.7
Joint disorder	12	9	1	0	29.3	13.3
Pain in extremity	9	8	0	0	22.7	10.7
Peripheral sensory neuropathy	11	1	0	0	16.0	1.3
Seroma	7	0	2	0	12.0	2.7
Pain [other]	4	3	1	0	10.7	5.3
Musculoskeletal disorder	4	1	0	0	6.7	1.3
Fatigue	0	2	2	0	5.3	5.3
Wound infection [with normal or Grade 1-2 ANC]	0	2	2	0	5.3	5.3
Fracture	1	2	0	1	5.3	4.0
Skin disorder	2	2	0	0	5.3	2.7
Gait abnormal	4	0	0	0	5.3	0.0
Joint pain	4	0	0	0	5.3	0.0
Skin hyperpigmentation	4	0	0	0	5.3	0.0

Adverse events were graded by Common Terminology Criteria for Adverse Events, version 3.0.
Treatment-related: definitely, probably, or possibly related to protocol treatment (or with unknown relationship).
Late: >6 months after start of radiation therapy.

eTable 3. Comparison of Local and Central Review Histology

Local	Central Review												
	Epi	ES Mxy Chon	Leio	Lipo	LG Fib Myx	MPNST	Myxofib	Rhab	Scler Epi Fib	Syno	UPS	USC	Total
Epi	1	0	0	0	0	0	0	0	0	0	0	0	1
ES Myx Con	0	1	0	0	0	0	0	0	0	0	0	0	1
Leio	0	0	10	0	0	0	0	1	0	0	3	1	15
Lipo	0	0	2	23	0	0	3	0	0	0	6	0	34
LG Fib Myx	0	0	0	0	0	0	0	0	0	0	0	0	0
MPNST	0	0	0	0	0	1	0	0	0	0	0	0	1
Myxofib	0	0	0	0	0	0	1	0	0	0	0	0	1
Rhab	0	0	0	0	0	0	0	0	0	0	0	0	0
Scler Epi Fib	0	0	0	0	0	0	0	0	0	0	0	0	0
Syno	0	0	0	0	0	1	0	0	0	5	0	0	6
UPS	0	0	2	0	0	0	6	0	0	0	23	0	31
USC	0	0	0	0	1	2	10	0	1	2	7	5	28
Total	1	1	14	23	1	4	20	1	1	7	39	6	118

Epi, epithelioid sarcoma

ES Myx Con, extraskeletal myxoid condrosarcoma

Leio, leiomyosarcoma

Lipo, liposarcoma

LG Fib Myx, low grade fibromyxoid

MPNST, malignant peripheral nerve sheath tumor

Myxofib, myxofibrosarcoma

Rhab, rhabdomyosarcoma

Scler Epi Fib, sclerosing epithelioid fibrosarcoma

Syno, synovial sarcoma

UPS, undifferentiated pleomorphic sarcoma

USC, undifferentiated spindle cell sarcoma

Kappa statistic: 0.51 (95% confidence interval 0.41-0.61)

eTable 4. Comparison of Local and Central Review Histologic Grade

Local	Central Review			
	G1	G2	G3	Total
G1	10	13	2	25
G2	3	15	20	38
G3	0	4	61	65
Total	13	32	83	128

Kappa statistic: 0.43 (95% confidence interval 0.31-0.56)

eTable 5. Comparison of Local and Central Review R Status

Local	Central Review			
	R0	R1	R2	Total
R0	107	1	0	108
R1	3	18	0	21
R2	1	1	0	2
Total	111	20	0	131

Kappa statistic: 0.83 (95% confidence interval 0.71-0.96)

eTable 6. Alternative Multivariable Models for Overall Survival (n=112; 37 events)

Variable	Minimum AIC Model HR (95% CI); p-value	Alternative Model #1 HR (95% CI); p-value	Alternative Model #2 HR (95% CI); p-value	Alternative Model #3 HR (95% CI); p-value
Location (upper/other vs. lower extremity)	--	1.92 (0.94-3.92); p=0.07	--	--
Size, cm (> 20 vs. ≤ 20)	2.51 (1.12-5.59); p=0.03	2.32 (1.04-5.17); p=0.04	2.14 (0.96-4.76); p=0.06	2.17 (0.96-4.89); p=0.06
Grade (2-3 vs. 1)	3.49 (0.80-15.30); p=0.10	--	--	4.29 (0.97-19.05); p=0.06
Histology (others vs. leio or lipo or myxofib)	2.24 (1.12-4.45); p=0.02	2.45 (1.22-4.91); p=0.01	2.46 (1.22-4.94); p=0.01	--
Histology (others vs. leio or myxoid/rc lipo or myxofib)	--	--	--	2.01 (1.00-4.03); p=0.05
Tumor viability (>0% vs. 0%) [1]	Cannot estimate; p=0.01	Cannot estimate; p=0.005	Cannot estimate; p=0.004	Cannot estimate; p=0.01
AIC	261.771	262.570	263.542	263.166

HR, hazard ratio; CI, confidence interval; leio, leiomyosarcoma; lipo, liposarcoma; myxofib, myxofibrosarcoma; rc, round cell; AIC, Akaike Information Criterion.

[1] There are no events in the 0% tumor viability group so the hazard ratio and p-value cannot be estimated by the Cox model. The p-value comes from the log-rank test stratified by study and the covariates in that model.

All tumor viability data, 94% of grade data, and 94% of histology data were based on central review; all other data were from the treating institution.

eTable 7. Alternative Multivariable Models for Disease-Free Survival (n=112; 51 events)

Variable	Minimum AIC Model HR (95% CI); p-value	Alternative Model #1 HR (95% CI); p-value	Alternative Model #2 HR (95% CI); p-value	Alternative Model #3 HR (95% CI); p-value
Zubrod PS (1 vs. 0)	1.64 (0.87-3.10); p=0.13	--	1.56 (0.82-2.97); p=0.17	1.82 (0.97-3.41); p=0.06
Location (other vs. lower/upper extremity)	1.93 (0.85-4.40); p=0.12	1.87 (0.83-4.23); p=0.13	--	1.79 (0.79-4.07); p=0.17
Size, cm (> 16 vs. ≤ 16)	2.63 (1.42-4.88); p=0.002	2.81 (1.50-5.26); p=0.001	2.43 (1.34-4.41); p=0.004	2.23 (1.22-4.09); p=0.009
Grade (2-3 vs. 1)	--	1.80 (0.66-4.89); p=0.25	1.71 (0.62-4.69); p=0.30	--
Histology (others vs. lipo or myxofib)	2.42 (1.23-4.76); p=0.01	2.45 (1.25-4.79); p=0.009	2.20 (1.10-4.37); p=0.03	--
Histology (others vs. myxoid/rc lipo or myxofib)	--	--	--	1.91 (0.95-3.87); p=0.07
Tumor viability (>0% vs. 0%)	4.91 (1.51-15.93); p=0.008	4.42 (1.36-14.32); p=0.01	4.79 (1.47-15.59); p=0.009	4.94 (1.52-16.07); p=0.008
AIC	362.014	362.742	363.032	365.422

HR, hazard ratio; CI, confidence interval; PS, performance status; lipo, liposarcoma; myxofib, myxofibrosarcoma; rc, round cell; AIC, Akaike Information Criterion.

All tumor viability data, 94% of grade data, and 94% of histology data were based on central review; all other data were from the treating institution.

eTable 8. Alternative Multivariable Models for Distant Disease-Free Survival

(n=112; 47 events)

Variable	Minimum AIC Model HR (95% CI); p-value	Alternative Model #1 HR (95% CI); p-value	Alternative Model #2 HR (95% CI); p-value	Alternative Model #3 HR (95% CI); p-value
Zubrod PS (1 vs. 0)	2.02 (1.06-3.87); p=0.03	2.03 (1.05-3.93); p=0.04	2.41 (1.29-4.52); p=0.006	2.19 (1.15-4.17); p=0.02
Location (other vs. lower/upper extremity)	2.15 (0.94-4.91); p=0.07	--	2.10 (0.92-4.81); p=0.08	2.04 (0.89-4.66); p=0.09
Size, cm (> 16 vs. ≤ 16)	2.78 (1.49-5.18); p=0.001	2.46 (1.35-4.49); p=0.003	2.60 (1.40-4.85); p=0.003	2.55 (1.37-4.74); p=0.003
Histology (others vs. leio or lipo or myxofib)	1.78 (0.94-3.38); p=0.08	1.77 (0.92-3.39); p=0.09	--	--
Histology (others vs. leio or myxoid/rc lipo or myxofib)	--	--	--	1.45 (0.77-2.74); p=0.25
Tumor viability (>0% vs. 0%)	4.33 (1.32-14.14); p=0.02	4.55 (1.39-14.87); p=0.01	4.97 (1.53-16.11); p=0.008	4.45 (1.35-14.61); p=0.01
AIC	336.863	337.778	338.040	338.680

HR, hazard ratio; CI, confidence interval; PS, performance status; leio, leiomyosarcoma; lipo, liposarcoma; myxofib, myxofibrosarcoma; rc, round cell; AIC, Akaike Information Criterion.

All tumor viability data and 94% of histology data were based on central review; all other data were from the treating institution.

eTable 9. Alternative Multivariable Models for Distant Metastasis (n=112; 40 events)

Variable	Minimum AIC Model HR (95% CI); p-value	Alternative Model #1 HR (95% CI); p-value	Alternative Model #2 HR (95% CI); p-value	Alternative Model #3 HR (95% CI); p-value
Zubrod PS (1 vs. 0)	2.45 (1.25-4.82); p=0.009	2.28 (1.15-4.52); p=0.02	2.28 (1.14-4.56); p=0.02	2.15 (1.06-4.36); p=0.03
Location (other vs. lower/upper extremity)	2.25 (0.92-5.49); p=0.08	--	--	--
Size, cm (> 16 vs. ≤ 16)	2.74 (1.40-5.33); p=0.003	2.56 (1.34-4.90); p=0.005	2.40 (1.27-4.53); p=0.007	2.57 (1.34-4.91); p=0.004
Grade (2-3 vs. 1)	--	1.91 (0.63-5.77); p=0.25	--	--
Histology (others vs. lipo or myxofib)	--	--	--	1.63 (0.78-3.38); p=0.19
Histology (others vs. myxoid/rc lipo or myxofib)	--	--	1.47 (0.69-3.13); p=0.31	--
Tumor viability (>0% vs. 0%)	4.09 (1.25-13.36); p=0.02	3.92 (1.19-12.93); p=0.02	3.98 (1.21-13.16); p=0.02	3.99 (1.21-13.12); p=0.02
AIC	293.219	294.515	294.924	294.243

HR, hazard ratio; CI, confidence interval; PS, performance status; lipo, liposarcoma; myxofib, myxofibrosarcoma; rc, round cell; AIC, Akaike Information Criterion.

All tumor viability data, 94% of grade data, and 94% of histology data were based on central review; all other data were from the treating institution.