

Supplementary Appendix

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

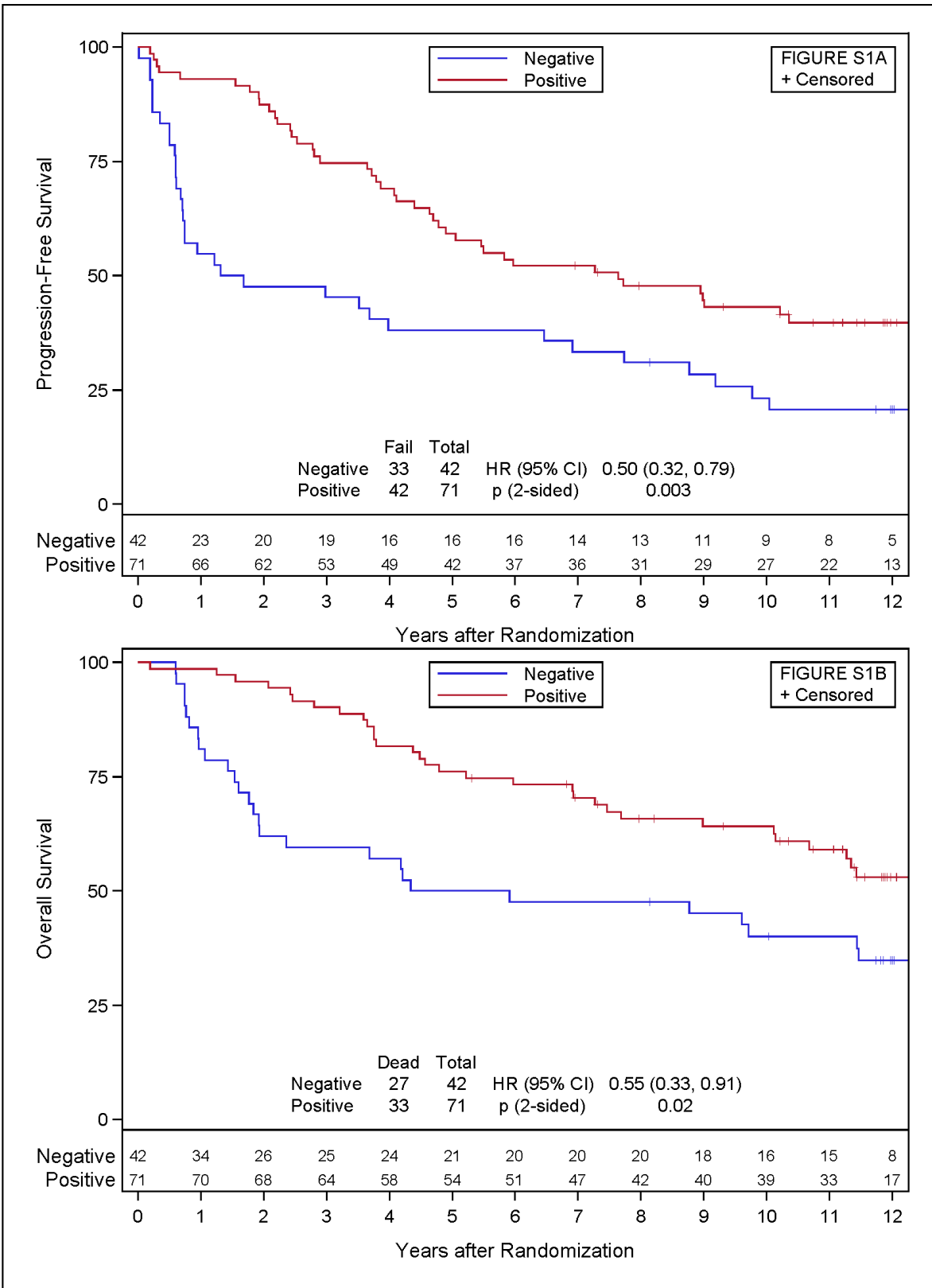
Supplement to: Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 2016;374:1344-55. DOI: 10.1056/NEJMoa1500925

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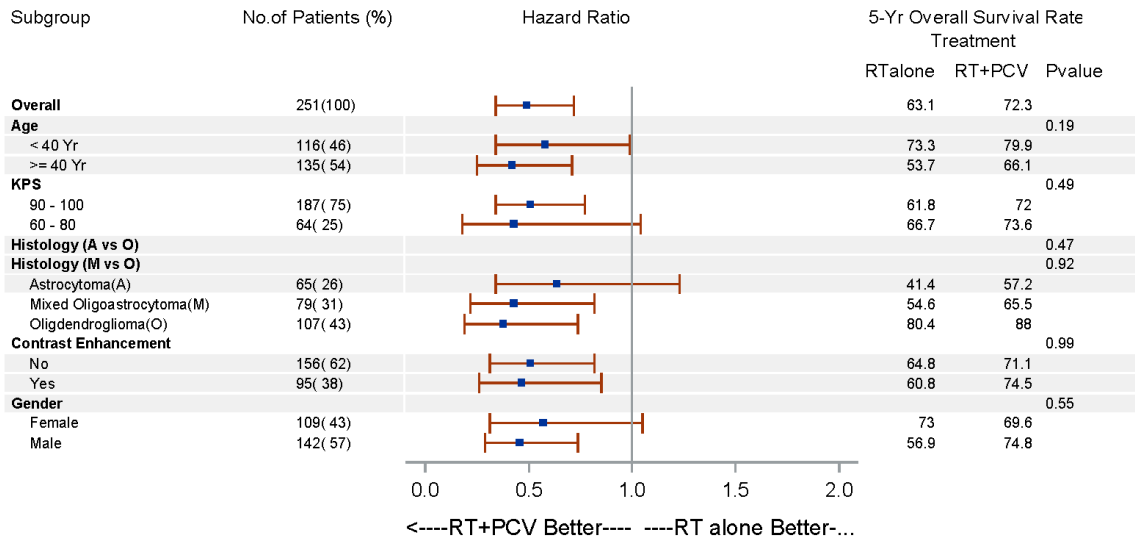
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Forest Plot of Hazard Ratios by Patient Subgroups



Due to time-varying treatment effect, hazard ratios are for treatment with > 1 year of follow-up
 The p-value is from the test statistic for testing the interaction between the treatment with > 1 year of follow-up and any subgroup variable

Table S1. Neurologic Function (NF) Status.

NF	Definition
0	No neurologic symptoms; fully active at home/work without assistance.
1	Minor neurologic symptoms; fully active at home/work without assistance.
2	Moderate neurologic symptoms; fully active at home/work but requires assistance.
3	Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4	Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

Table S2. Frequency of IDH1 132H Mutations by Histologic Type.

IDH	Astrocytoma		Mixed		Oligodendroglioma		Total	
	n	%	n	%	n	%	n	%
Negative	13	52.0	18	46.2	11	22.4	42	37.2
Positive	12	48.0	21	53.8	38	77.6	71	62.8

Table S4. Sensitivity Analyses to Assess Effect of Patients Lost to Follow Up on the Treatment Effect for Overall Survival.

	Cases changed to deaths	Median survival (95% CI)		10 year estimates		Log-rank p-value
		RT alone	RT+PCV	RT alone	RT+PCV	
1) Keep patients lost to follow-up as censored	0	7.8 (6.1, 9.8)	13.3 (10.6, NR)	40.1%	60.1%	0.002
2) Change patients lost to follow-up on RT+PCV arm	26	7.8 (6.1, 9.8)	9.7 (7.7, 11.66)	40.1%	49.6%	0.3159
3) Change patients lost to follow-up on RT alone arm	14	7.1 (6.0, 9.0)	13.3 (10.6, NR)	35.7%	60.1%	<0.0001
4) Change all patients lost to follow-up	40	7.1 (6.0, 9.0)	9.7 (7.7, 11.6)	35.7%	49.6%	0.0313
5) Change patients lost to follow-up on RT+PCV arm (to balance number lost on each arm)	12	7.8 (6.1, 9.8)	11.6 (8.5, NR)	40.1%	56.5%	0.0183

Table S5. Post-progression Treatment by Treatment Arm.

	RT Alone (n=126)	RT + PCV (n=125)
Cases with progression	92 (73%)	49 (39%)
	n	n
Resected	33 (26%)	17 (14%)
Salvage chemotherapy	71 (56%)	29 (23%)
Salvage radiotherapy/radiosurgery	24 (19%)	7 (6%)

RT=radiation therapy

PCV= procarbazine, CCNU, and vincristine

Table S6. RTOG/EORTC Late Radiation Morbidity Scoring Scheme.

Organ Tissue	0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	Death directly related to radiation effects
Subcutaneous Tissue	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis	
Mucous Membrane	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	
Salivary Glands	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	
Spinal Cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	
Brain	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	
Eye	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panophthalmitis/Blindness	
Larynx	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	
Lung	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis severe cough); Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/continuous O2/Assisted ventilation	
Heart	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST Changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low QRS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	
Esophagus	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing; Dilation required	Necrosis/Perforation Fistula	

Organ Tissue	0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Small/Large Intestine	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	
Liver	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	
Kidney	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%; Creatinine 1.5-2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%	
Bladder	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis	
Bone	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
Joint	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	