



ERCC1 gene expression is associated with outcome in stage II-III esophageal adenocarcinoma patients treated with preoperative platinum-based chemoradiation in a phase II cooperative group study (S0356)



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Introduction

Preoperative platinum-based chemoradiation for operable esophageal cancer has improved overall survival (OS) compared to surgery alone. The phase II SWOG 0356 trial was designed to test oxaliplatin (OXP) plus infusion 5-fluorouracil (5-FU) and external beam radiation prior to surgery for potentially curable esophageal adenocarcinoma and has produced a promising centrally confirmed complete pathologic response (pCR) rate (28.2%). After surgery, patients were given post-operative OXP and 5FU. Two-year OS was 54.2%.

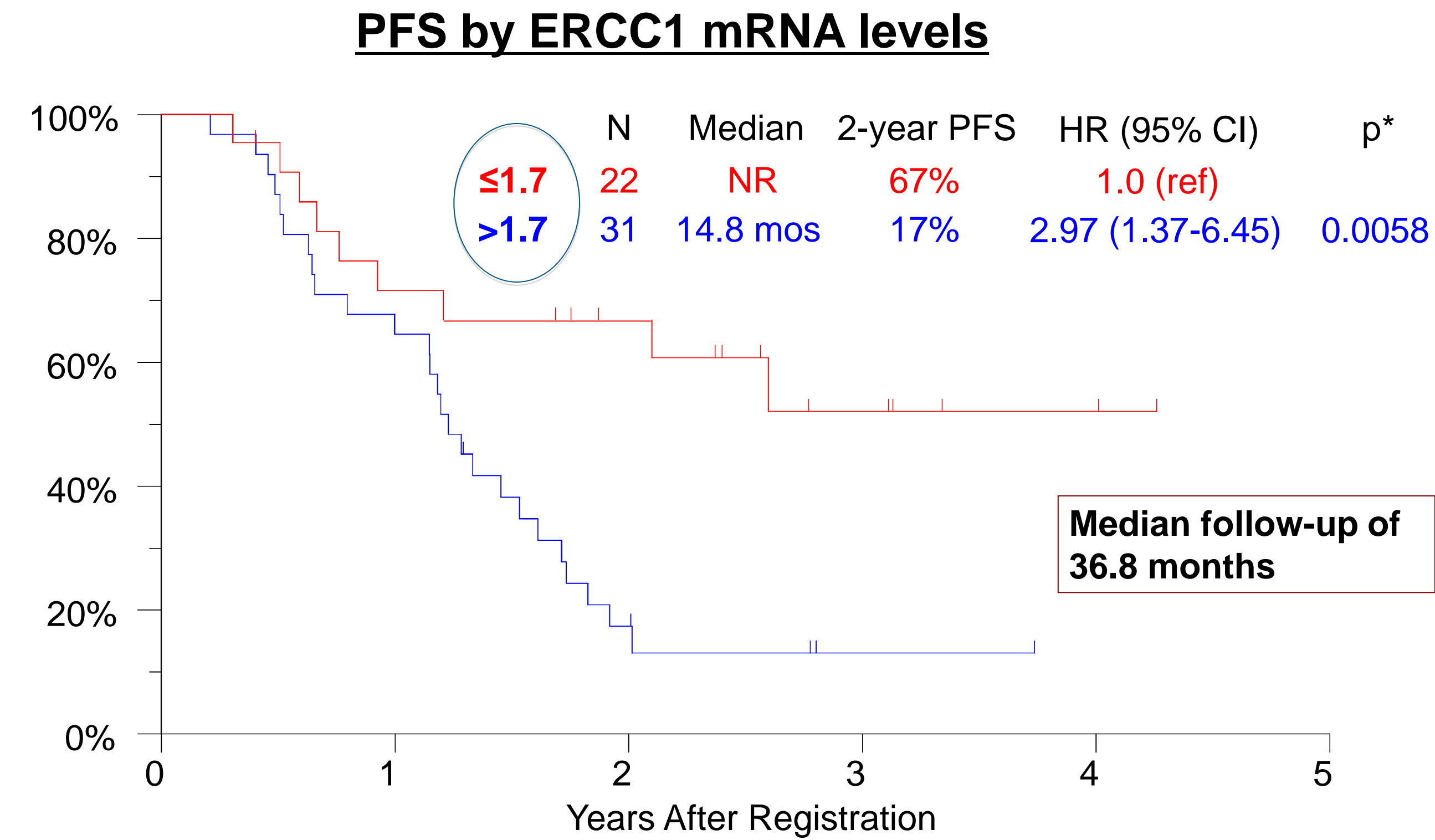
We tested whether intratumoral gene expression (GE) levels of genes in drug metabolism (DPD, GSTP1, TS and TP) and DNA repair (ERCC1 and XPD) predicted clinical outcome. We also tested whether a specific pattern of 13 polymorphisms in 8 genes involved in either drug metabolism (GSTP, MTHFR and TS) or DNA repair (ERCC1, RAD51, XPD, XRCC1 and XRCC3) predicted clinical outcome.

Results

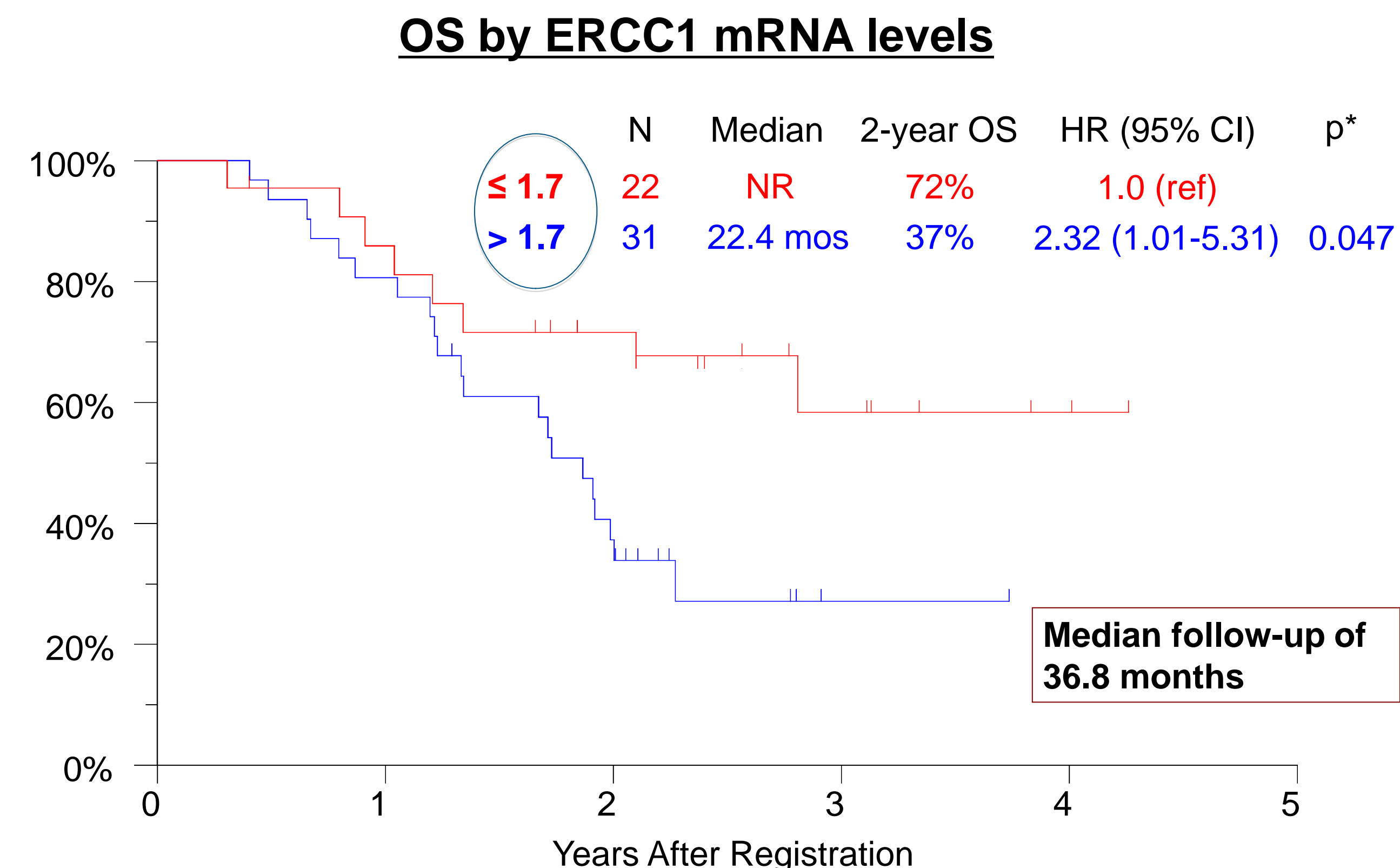
In univariate analysis, our results demonstrated that ERCC1 mRNA levels were significantly associated with progression-free survival (PFS) and OS. Patients with ERCC1 mRNA levels above the pre-defined cutoff of 1.7 (ERCC1 high) had worse 2-year PFS (17 vs 67%, $p=0.0058$) and 2-year OS (37 vs 72%, $p=0.047$) compared to patients with ERCC1 mRNA levels below the pre-defined cutoff of 1.7 (ERCC1 low). ERCC1 mRNA levels were not associated with pCR. Adjustment for baseline characteristics did not affect the results.

An analysis of PFS using a recursive partitioning model found the optimal split for ERCC1 gene expression to be 1.66 (adjusted $p=0.04$). This result further validates our predefined cutoff of 1.7.

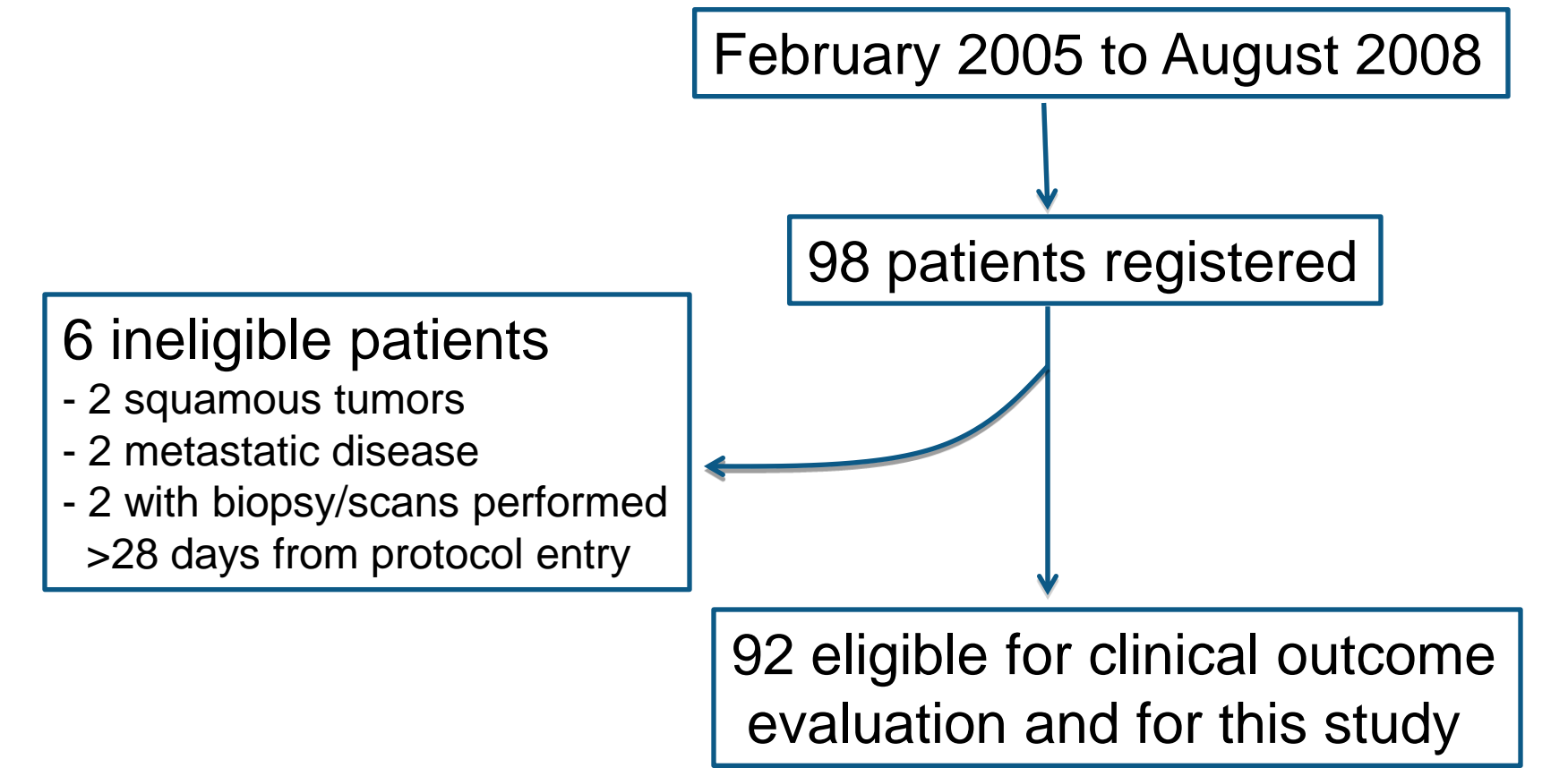
The other genes analyzed for their mRNA levels tested did not demonstrate significant associations with clinical outcome. The polymorphisms analyzed also failed to show any association with clinical outcome.



*p-value unadjusted for multiple comparisons



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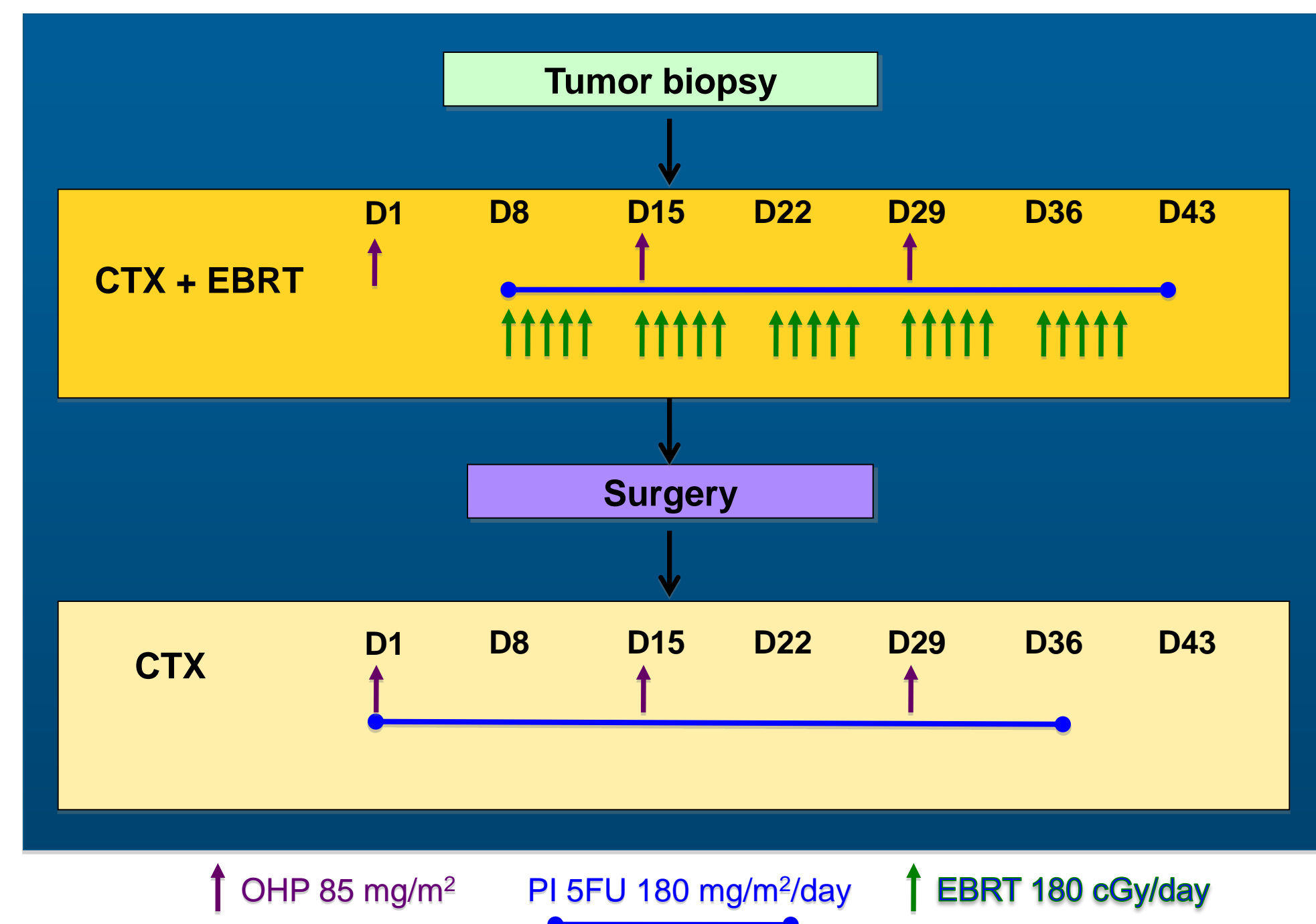
Patient characteristics

	Overall (N=92)	Gene Expression Dataset (N=55)
Median age (range)	62.0 (41.6-83.1)	63.9 (43.6-83.1)
Gender		
Male	86 (93%)	51 (93%)
Female	6 (7%)	4 (7%)
Race		
White	85 (96%)	51 (94%)
Other	4 (4%)	3 (6%)
Missing	3	1
Performance status		
0/1	54/37 (59%/41%)	34/21 (62%/38%)
Missing	1	0
Primary Site		
Esophagus	54 (60%)	34 (62%)
GE Junction	36 (40%)	21 (38%)
Missing	2	0
pCR	26 (28%)	14 (25%)

Methods

A total of 92 patients from the SWOG S0356 study were eligible for this molecular correlative study. mRNA was extracted utilizing manually-microdissected tumor tissue. After cDNA was prepared by reverse transcription, quantitation of the candidate genes and an internal reference gene (β -actin) was performed using a fluorescence-based real-time detection method (TaqMan). Established GE cutoffs were tested (ERCC1 $<1.7 \times 10^{-3}$ normalized expression units; TS $<4.0 \times 10^{-3}$ normalized expression units). DNA was extracted from blood and genotyped using PCR-RFLP techniques.

SWOG S0356 treatment plan



Conclusions

Our data suggests that ERCC1 mRNA levels may identify the patients with stage II-III esophageal adenocarcinoma that are likely to experience longer survival when treated with preoperative OXP-based CRT. Based on these results, SWOG is planning a prospective biomarker-driven clinical trial.