

Supplementary Appendix

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

Supplement to: Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513-20.

On Line Supplement

A number of unplanned secondary analyses were performed at the request of the statistical reviewer. Two different *per protocol* analyses were undertaken. The first excluded 21 patients who did not receive or complete the intended treatment: four who did not receive radiation, 15 who did not receive the intended treatment as a result of crossover, and two who did not complete the intended treatment. The second *per protocol* analysis excluded 117 patients: the 21 described above plus an additional 96 patients who were lost to follow-up, mostly in the later years.

A number of sensitivity analyses were also performed to look at the potential impact of patients lost to follow-up. In the first, we used imputation based on treatment-specific annual hazard rates to randomly “assign” recurrences and estimate failure times for those lost to follow-up. In addition, we performed a second analysis where we assumed that the annual hazard rates were higher in the patients lost to follow-up (using the upper limit of the 95% confidence interval for the hazard rate in that year). Each of these analyses was run 1000 times and the estimates were averaged.

We performed two other analyses to look at the impact of censoring. In the first, a composite outcome of local recurrence or death was analyzed. In the second analysis, a cumulative event analysis was performed considering any recurrence (local, regional or distant), new second primary cancer (including contralateral breast cancer) or death as an event.

Outcome and Analysis Set	10-Year Cumulative Incidence (%)		Absolute Difference (%) 95% CI
	Control	Hypofractionated	
Local Recurrence:			
Full Analysis Set (n = 1234)	6.7	6.2	0.5 (-2.5, 3.5)
Per Protocol Set #1 (n = 1213)	6.6	6.2	0.3 (-2.6, 3.3)
Per Protocol Set #2 (n = 1117)	6.9	6.6	0.3 (-2.8, 3.4)
Sensitivity Analysis #1	6.9	6.6	0.4 (-2.4, 3.5)
Sensitivity Analysis #2	7.0	6.8	0.3 (-2.7, 3.2)
Composite Outcomes:			
Local Recurrence or Death	20.0	19.3	0.7 (-3.9, 5.2)
Any Recurrence, Second Primary or Death	29.6	30.3	-0.7 (-5.9, 4.5)

The *per protocol* and sensitivity analyses are consistent with the main analysis of the trial. They support that the results of the trial are robust despite the limited protocol deviations and the patients lost to follow-up. In the time-to-event analyses of the composite outcomes, the overall event rates are higher, as expected. However, the results are consistent with the original hypothesis that hypofractionated breast irradiation is not inferior to the standard longer fractionated regimen.