Supplementary Appendix

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

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Participating Cooperative Groups

Participating centres include those associated with the NCIC Clinical Trials Group (NCIC CTG), National Surgical Adjuvant Breast and Bowel Project (NSABP), North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG), and Trans Tasman Radiation Oncology Group (TROG).

Ineligibility criteria

Patients were ineligible from the trial for the following reasons: (1) the clinical evidence of T4 or N2-3 disease prior to surgery; (2) residual clinical disease in the axilla following dissection; (3) presence of a serious non-malignant disease (e.g. systemic lupus erythematosis, scleroderma, cardiovascular or pulmonary disease) which would preclude definitive radiation therapy; (4) currently pregnant or lactating; (5) concurrent or previous malignancies; (6) psychiatric or addictive disorders, which precluded obtaining informed consent or adherence to protocol; and (7) inability to receive radiotherapy within 8 weeks of completing adjuvant chemotherapy or within 16 weeks after the last surgical breast procedure for patients receiving endocrine therapy only.

Planning details for whole breast irradiation

For patients assigned to whole breast irradiation (WBI), the aim was to treat the breast with a parallel opposed pair of fields tangentially arranged across the chest. Standard borders were recommended: medial border – mid-sternum, lateral border – mid-axillary line, superior border – below the clavicle, and the inferior border – 1-1.5 cm below the infra-mammary crease. CT planning was recommended. Patients were treated with 4-18 megavoltage radiation in the supine position with the arm abducted. Wedges or compensators were used to ensure uniform dose of +/- 7%. The dose was prescribed at a point mid-separation 2/3 the distance between the skin and the base of the tangents. Treatment beam images were obtained to confirm adequate coverage.

Radiation Quality Assurance

MA.20 employed an extensive quality assurance program to confirm that patients were treated in compliance with the protocol. This included: (1) a review of treatment centres' facilities and practice run – prior to initiating the study, each centre was asked to plan a patient using the experimental technique described in the protocol. Copies of the treatment prescription, calculation sheets, isodose distributions, and digitally reconstructed radiographs were couriered to one of two central review centres to confirm if the patient could be treated in compliance with the protocol; (2) real-time review – each centre was asked to send similar information on the first 25 patients randomized in the trial. Any deviations from protocol observed were communicated to the treatment centre with suggestions to modify treatment accordingly. When centres had documented their 15^{th} consecutive patient could be treated with no protocol deviations, real-time review was no longer required; and (3) final review – for patients who did not complete real-time review, similar information as above (treatment prescription, isodose distribution, etc.) was reviewed upon completion of treatment.

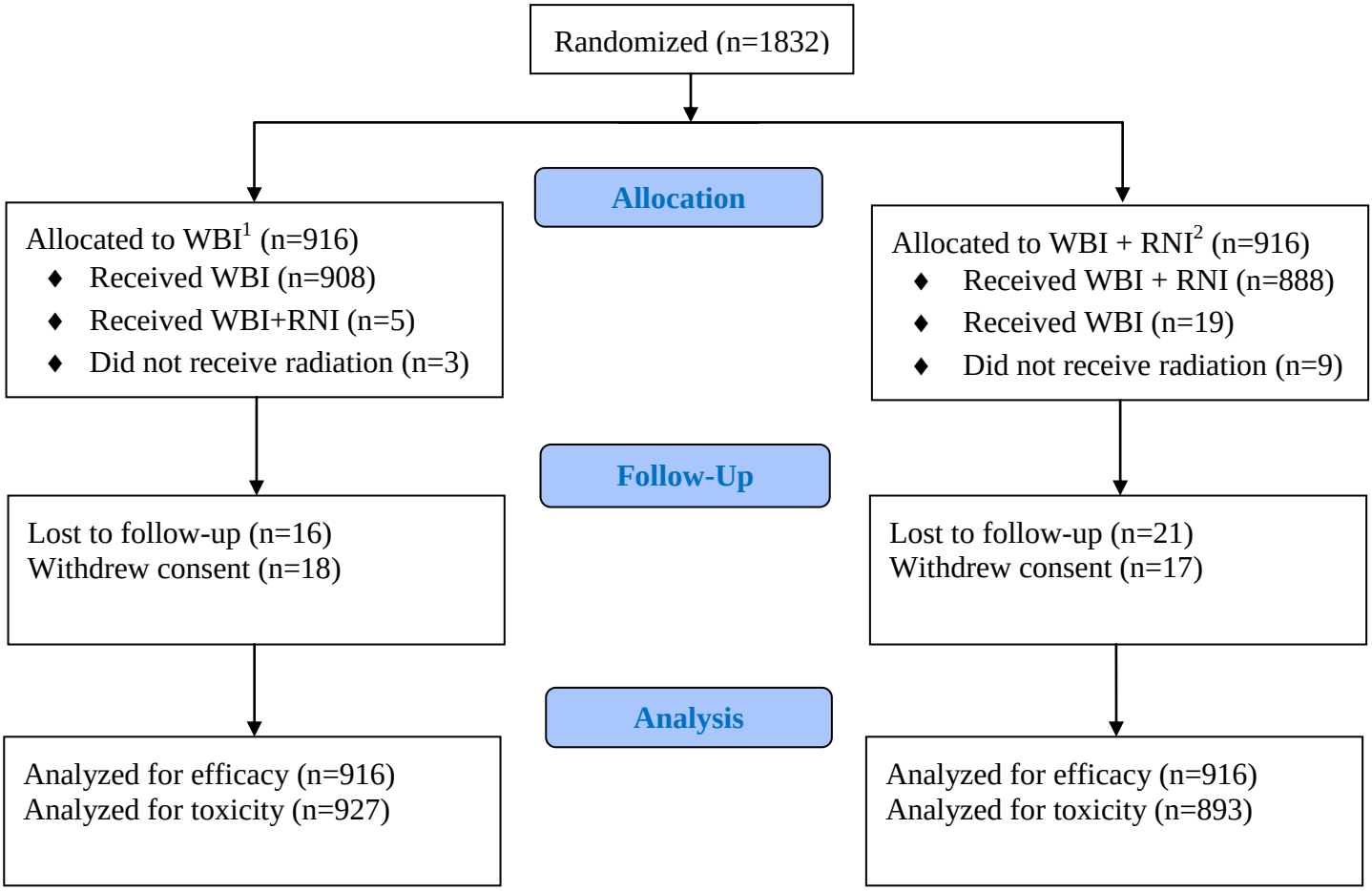
Follow-up

Follow-up visits occurred during the last week of radiotherapy, at month 3 and 9 after the last dose of radiotherapy, then every 6 months for two years, and then annually. At each visit, a history and physical were performed and adverse events were assessed by the NCI Common Toxicity Criteria version 2. Mammograms were performed 6 months after radiotherapy and then annually.

Censoring

Overall survival (OS) was defined as time from randomization to death from any cause; censoring was at last contact. Disease-free survival (DFS) was defined as time from randomization to time of first recurrence in the ipsilateral breast, nodal or distant sites, contralateral breast cancer or breast cancer death: censoring was at last contact or non breast cancer death. Isolated locoregional disease-free survival (ILDFS) was defined as time from randomization to time of first recurrence of cancer in the ipsilateral breast, axillary, supraclavicular, or internal mammary nodes without evidence of distant disease within one month. Data was censored at the time of distant recurrence as a first recurrence or within 30 days, last contact, or non breast death, which ever occurred first. Distant disease-free survival (DDFS) was defined as time from randomization to time of recurrence at a distant site (bone, liver, lung or CNS) or breast cancer death. Data was censored at last contact or non breast death.

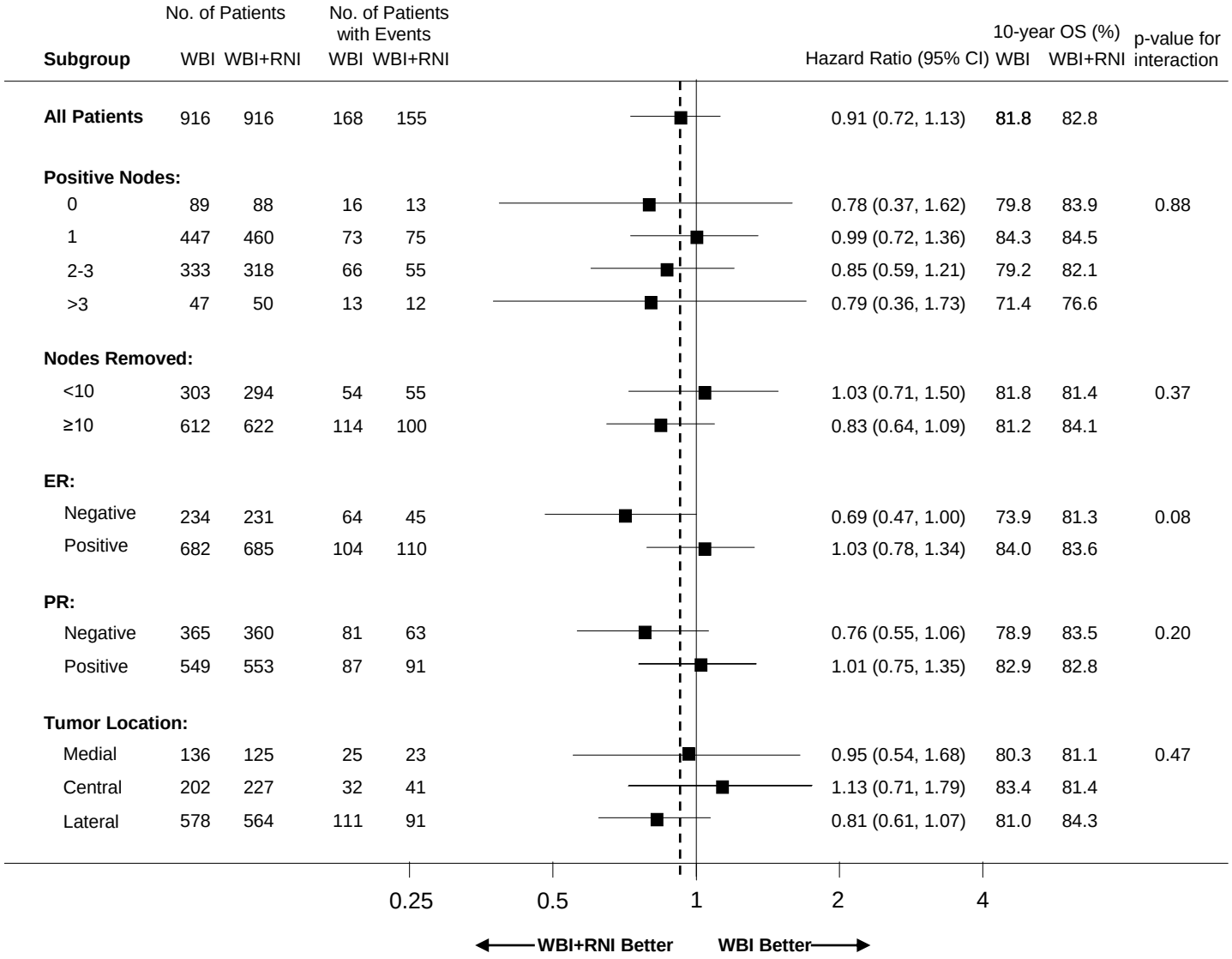
Figure S1. CONSORT Diagram for Randomization, Treatment and Follow-up



For patients who were lost to follow-up or withdrew consent, data on disease recurrence and death was included to that point in time.

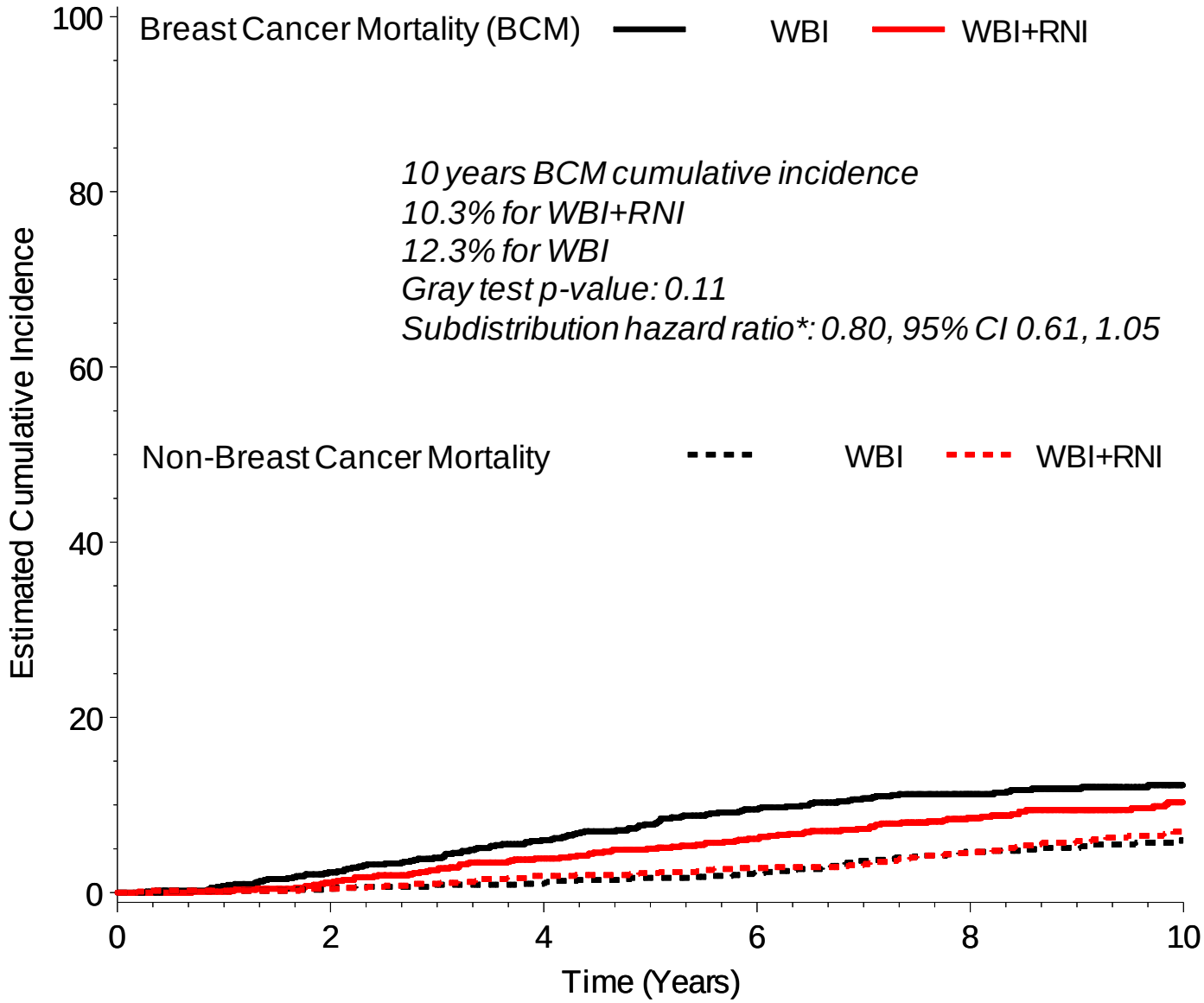
[1] WBI – whole breast irradiation; [2] WBI + RNI – whole breast irradiation + regional nodal irradiation.

Figure S2. Hazard Ratios for Overall Survival in Subgroups of Patients



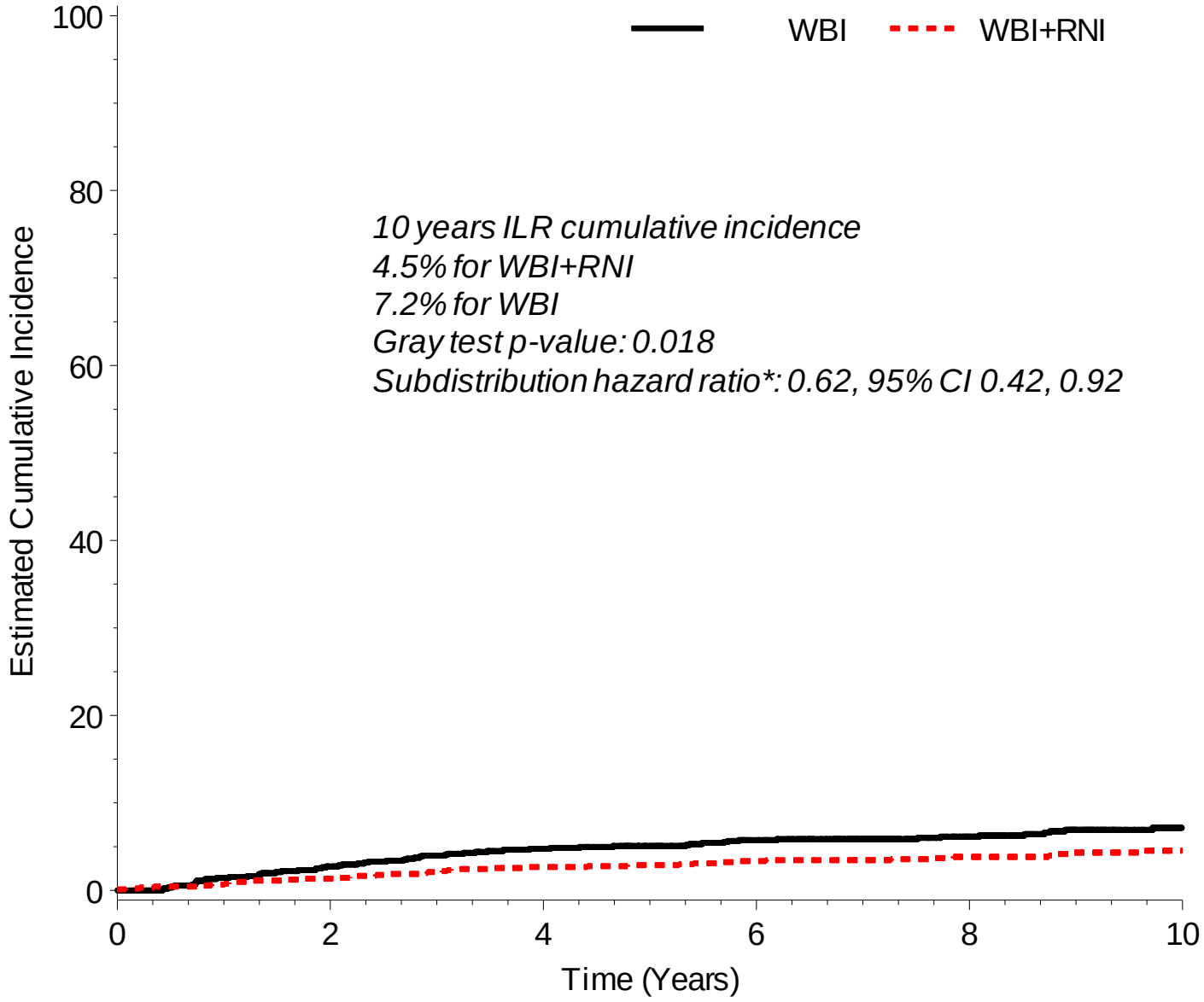
The dotted line at 0.91 indicates the overall hazard ratio estimate. The x-axis is scaled according to the logarithm of the hazard ratio.

Figure S3. Cause Specific Mortality by Treatment Assignment



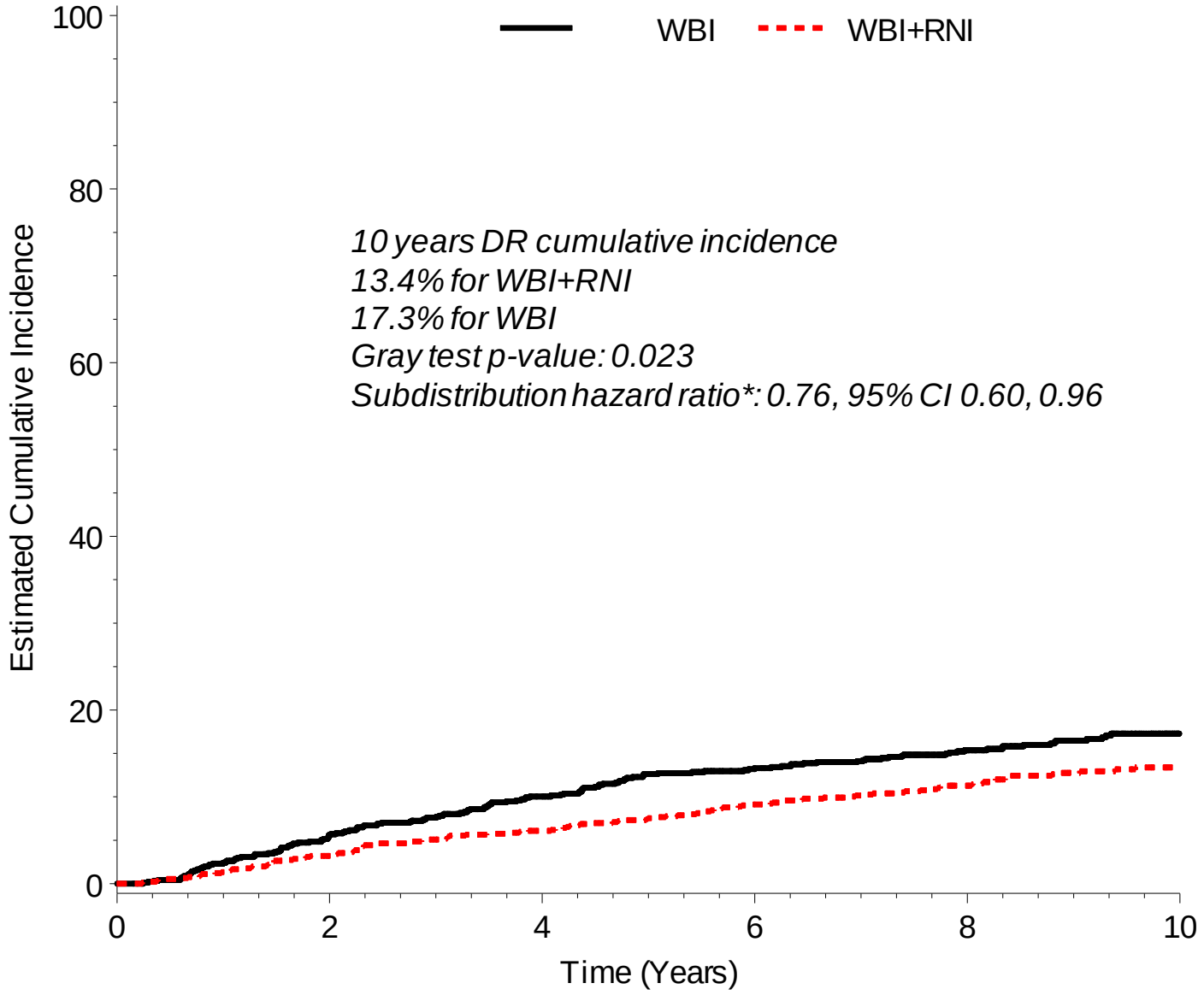
**based on* Fine JP and Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. *JASA* 94:496-509.

Figure S4. Cumulative Incidence of Isolated Locoregional Recurrence (ILR) by Treatment Assignment



**based on* Fine JP and Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. *JASA* 94:496-509.

Figure S5. Cumulative Incidence of Distant Recurrence (DR) by Treatment Assignment



**based on* Fine JP and Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. *JASA* 94:496-509.

Table S1. Baseline Characteristics of Patients (No. and %)

Characteristic	WBI N (%) 916 (100)	WBI+RNI N (%) 916 (100)
Age		
Median (Range) - yr	53 (26,84)	54 (29,84)
Initial sentinel lymph node biopsy[1]	357 (39)	360 (39)
Axillary nodes removed		
Median (Interquartile range)	12 (8,16)	12 (9,16)
1-9	303 (33)	294 (32)
$\geq$ 10	612 (67)	622 (68)
Missing	1 (0)	0 (0)
Positive axillary nodes		
None	89 (10)	88 (10)
1	447 (49)	460 (50)
2	233 (25)	209 (23)
3	100 (11)	109 (12)
> 3	47 (5)	50 (5)
Tumor size		
$\leq$ 2 cm	501 (55)	459 (50)
2.1-5 cm	409 (45)	443 (48)
> 5 cm	6 (1)	13 (1)
Missing	0 (0)	1 (0)
Lymphovascular invasion		
Absent	492 (54)	505 (55)
Present	381 (42)	378 (41)
Missing	43 (5)	33 (4)
SBR Tumor grade		
I-II	523 (57)	517 (56)
III	387 (42)	391 (43)
Missing	6 (0.7)	8 (0.9)
Estrogen receptor status		
Positive	682 (74)	685 (75)
Negative	234 (26)	231 (25)

Characteristic	WBI N (%) 916 (100)	WBI+RNI N (%) 916 (100)
Progesterone receptor status		
Positive	549 (60)	553 (60)
Negative	365 (40)	360 (39)
Missing	2 (0)	3 (0)
Adjuvant chemotherapy		
High dose anthracycline (e.g., CEF, FEC)	357 (39)	334 (37)
Anthracycline + taxane (e.g., ACT, FEC-D)	244 (27)	230 (25)
Anthracycline/no taxane (e.g., AC)	183 (20)	220 (24)
Other (e.g., CMF)	45 (5)	47 (5)
No chemotherapy	87 (9)	85 (9)
Adjuvant endocrine therapy[2]		
Aromatase Inhibitor[3]	529 (58)	521 (57)
Tamoxifen	167 (18)	172 (19)
No endocrine therapy	220 (24)	223 (24)
Boost irradiation[4]		
Yes	317 (35)	294 (32)

[1] Only 35 patients in WBI arm and 33 patients in WBI + RNI had a sentinel lymph node biopsy only.

[2] Endocrine therapy was initiated following radiation therapy in some patients.

[3]Aromatase inhibitor used solely or following Tamoxifen.

[4] Boost irradiation was delivered after WBI or WBI + RNI.