

Substantially lower lung cancer incidence with TARGIT-IORT (targeted intraoperative radiotherapy) compared with whole breast radiotherapy in the TARGIT-A randomised trial for breast cancer: 25-year update

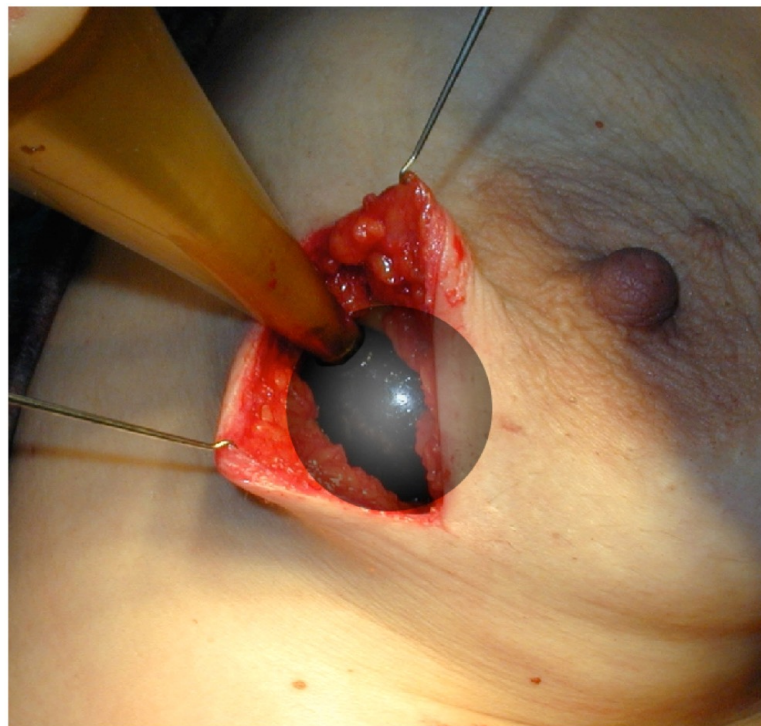
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91

Background External beam whole breast radiotherapy (EBRT) given after breast conserving surgery inevitably leads to carcinogenic irradiation of nearby vital organs such as the lungs. **TARGIT-A randomised trial (recruited from 2000-2012) found that TARGIT-IORT during the initial lumpectomy is as effective as EBRT in controlling breast cancer.**

TARGIT-IORT reduced pain, improved cosmetic outcome, quality of life, and reduce travel and cost.

- **Significantly fewer deaths from non-breast-cancer causes with TARGIT-IORT vs. whole breast radiotherapy (EBRT).**
- **TARGIT-IORT conferred an overall survival benefit in patients with grade 1 or 2 cancers: 12-year mortality reduction from 15% to 10.5%**



targit.org.uk



BMJ 2020



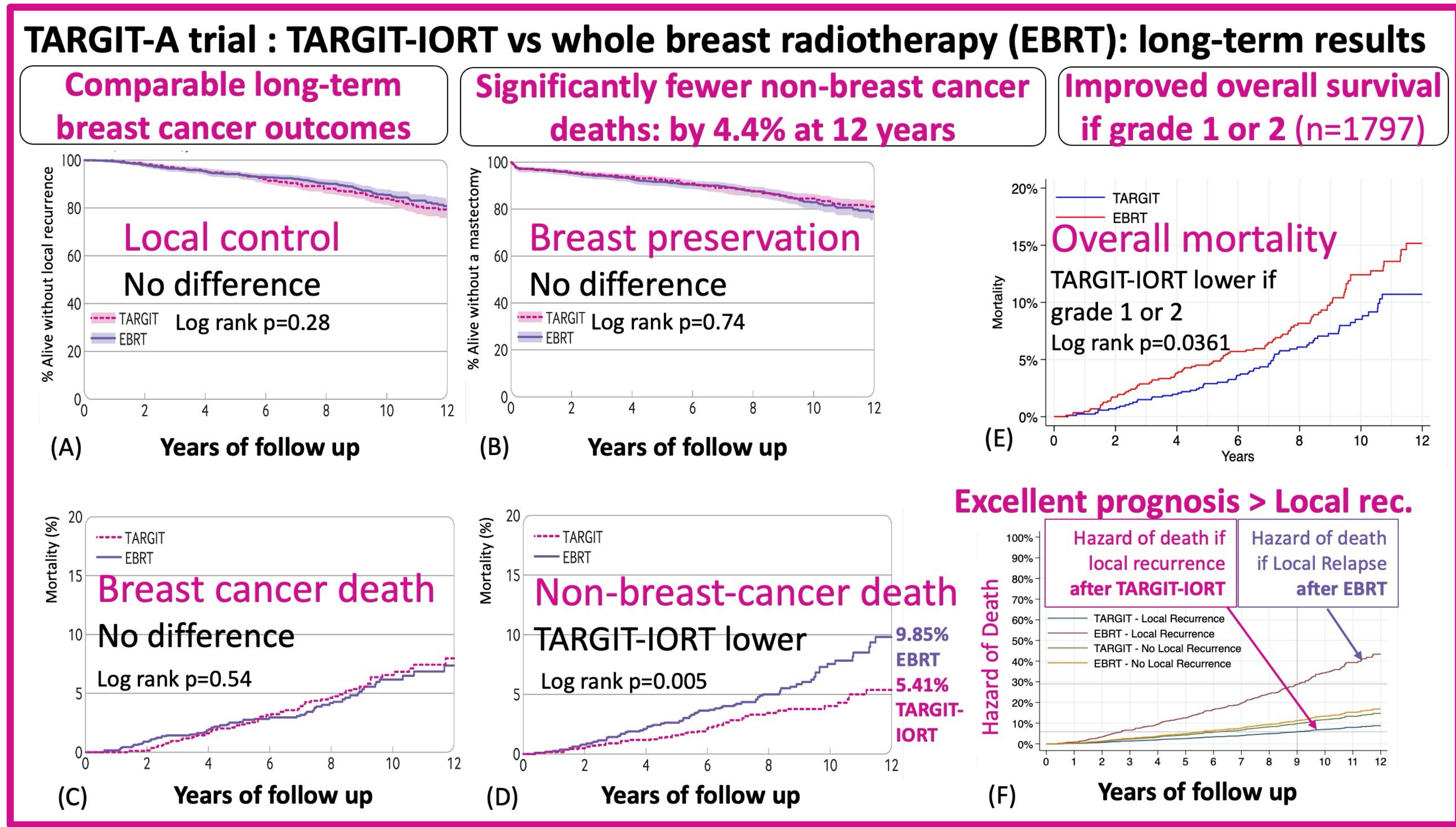
BJC 2021



Over 50,000 breast cancer patients in 260 centres from 38 countries have been treated with TARGIT-IORT



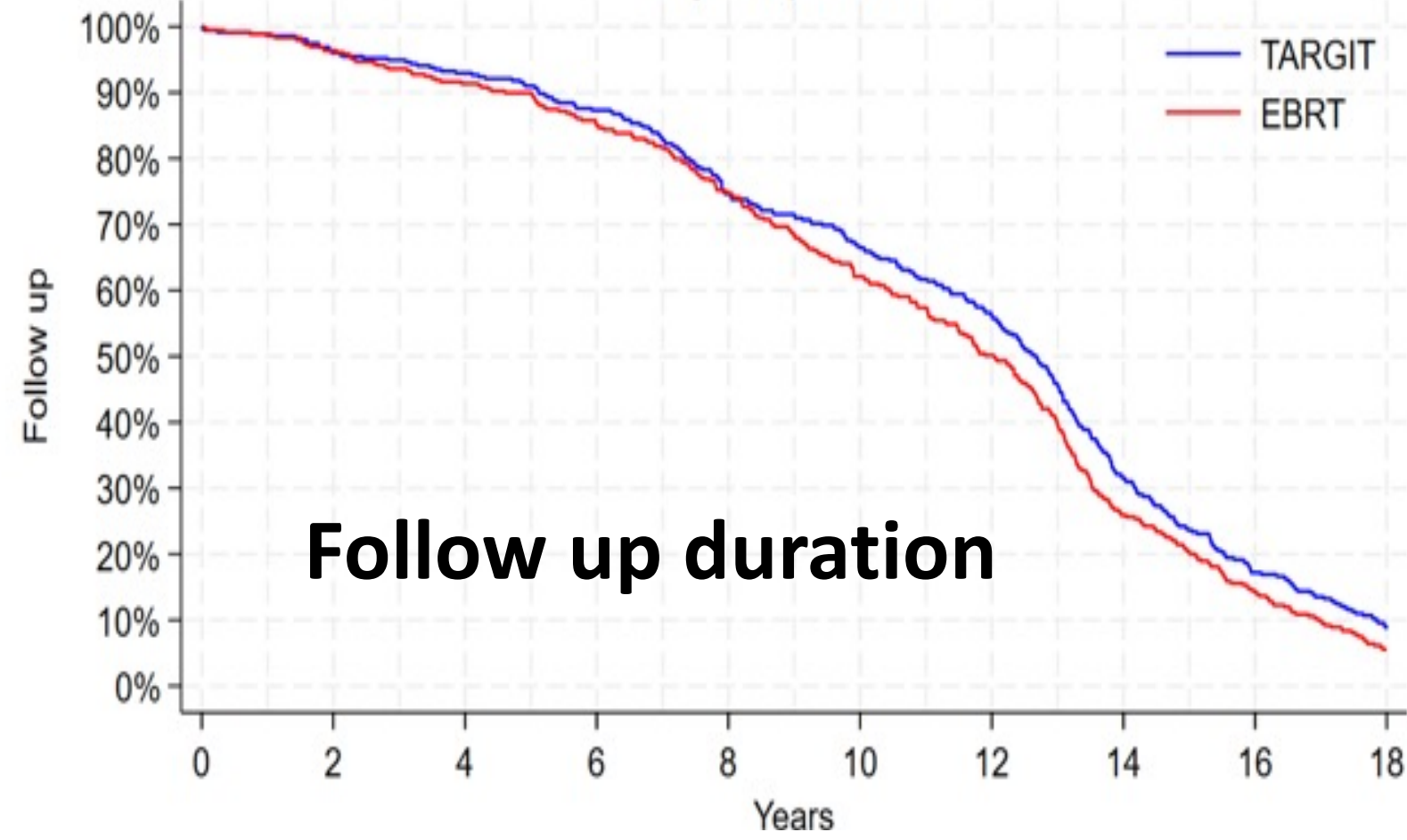
Previous results



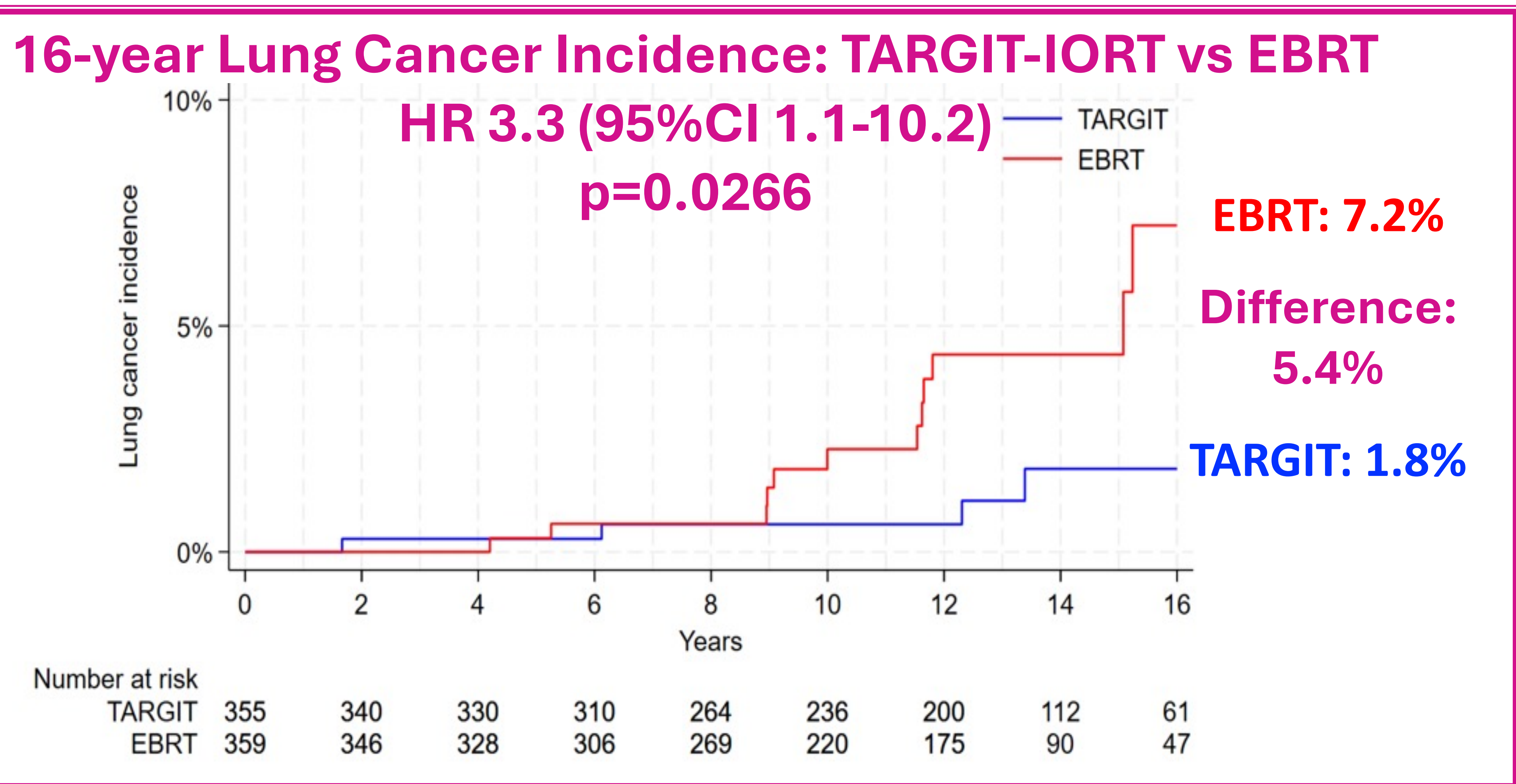
Material and methods

- We collected long term data about health status and new cancer diagnoses of UK patients from the TARGIT-A randomised trial, using direct patient contact, & NHS Digital data.
- We compared lung cancer incidence between patients randomised to TARGIT-IORT vs EBRT.

N.B. The duration of follow-up for patients receiving EBRT was slightly shorter vs TARGIT-IORT (p=0.0399). In other words, some cases of lung cancer in the EBRT group may have been missed, so the benefit of targeted intraoperative radiotherapy may have been underestimated.



New Results



Headline results

- Significantly more lung cancer with EBRT vs TARGIT-IORT
HR 3.3 (95%CI 1.1-10.2), p=0.0266
- 16-year incidence of lung cancer: EBRT: **7.2%** vs. TARGIT: **1.8%**
Reduction with TARGIT-IORT = 5.4% (95%CI 0.3 -10.5)

50,000 breast cancer patients could avoid getting lung cancer by taking TARGIT-IORT

*An estimated 920,000 breast cancer patients worldwide are suitable for TARGIT-IORT during lumpectomy, annually.

Using the 5.38% reduction in lung cancer risk that we have observed, if TARGIT-IORT were to be made accessible to these patients, then 49,496 (95%CI 5500-134320) of these patients would be spared the diagnosis of a lung cancer during their follow up.

Conclusions

- With very long-term follow data from of a large TARGIT-A randomised trial, we found a substantial increase in lung cancer incidence with EBRT vs TARGIT-IORT.
- It is a tragedy when women who outlive breast cancer then succumb to this frequently lethal radiation-induced lung cancer, which is avoidable by using TARGIT-IORT during lumpectomy instead of post-operative EBRT.
- These new data further mandate* full discussion about benefits of TARGIT-IORT vs. EBRT with patients, including reduction in lung cancer incidence, *before their surgery*, so they have a choice to take it during their initial surgical excision.

*Discussion about TARGIT-IORT as an option to EBRT is mandatory as per GMC guidance and the UK law (UK Supreme Court. Montgomery v Lanarkshire Health Board. 11 Mar 2015.

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A novel methodology using direct patient contact and UK national registries to collect long-term data from randomised trials: Extended follow up of the TARGIT-A trial of intraoperative radiotherapy for breast cancer (TARGIT-X)

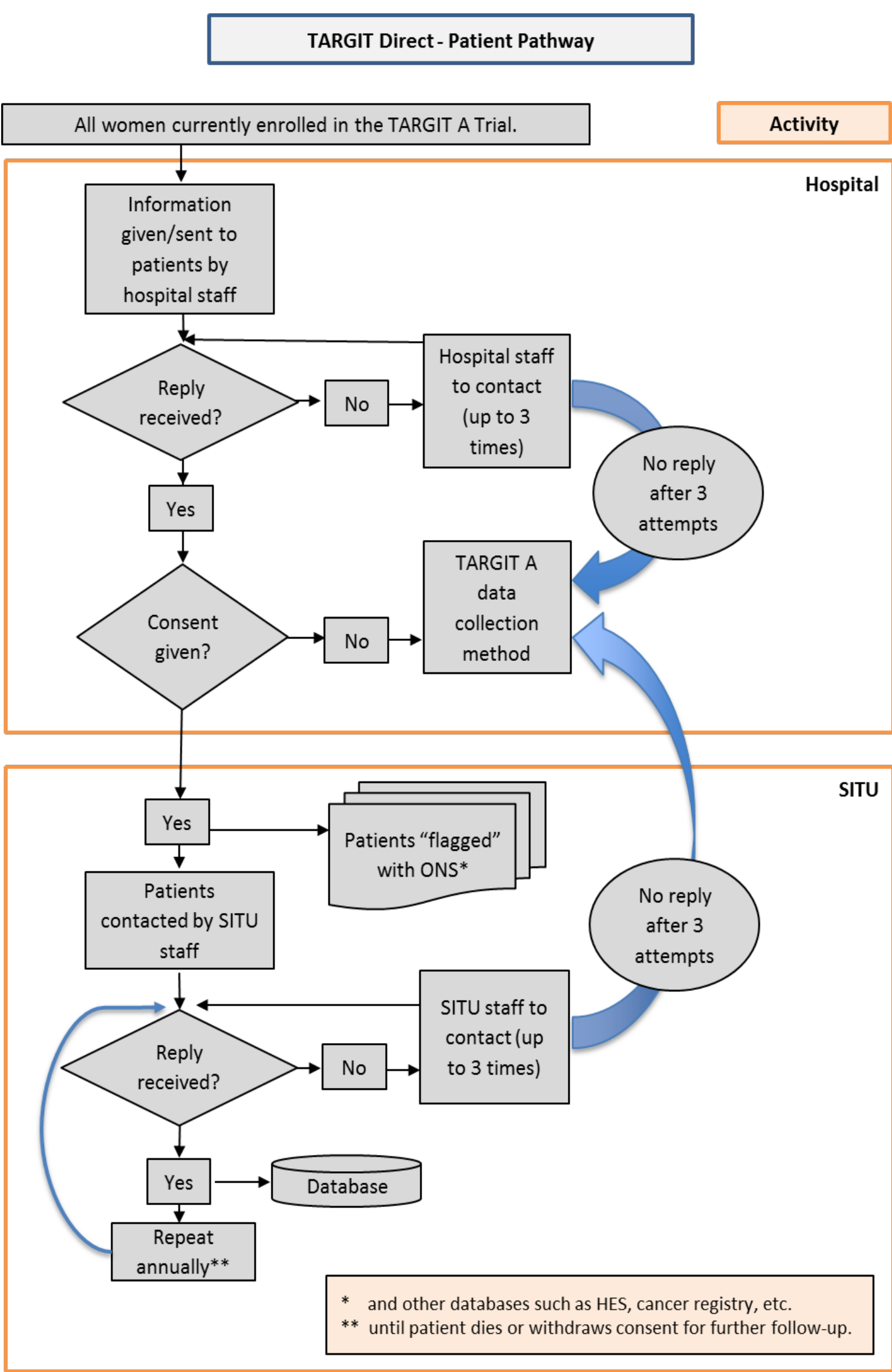
Full paper in press at NIHR Journals Library

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111

Introduction: Many diseases including breast cancer have a long natural history. Therefore, longer-term effects of treatments are important for patients and for their full evaluation. However, trial follow up data are collected by specific staff and funded for a relatively short duration. We evaluated whether we could collect follow up information for patients in a breast cancer randomised clinical trial by direct patient contact and data from national registries.

Setting: The TARGIT-A randomised clinical trials of targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) vs whole breast radiotherapy (EBRT_ and delayed TARGIT-IORT vs EBRT (n=1153), recruited women with early breast cancer diagnosed in 33 centres in 12 countries, between March 2000 to June 2012. We planned to recruit all UK patients from the TARGIT-A trials for extended follow-up. This was the first randomised trial of intraoperative radiotherapy for breast cancer.



TARGIT-IORT website



TARGIT-IORT literature



TARGIT-IORT BMJ paper



TARGIT-IORT BJC paper

Methods:

- We assessed the feasibility of recording whether patients are alive and their current health status including events related to breast cancer, and effects of radiotherapy such as lung cancer diagnoses, by direct patient contact and data from NHS Digital (health episodes, diagnoses and death).
- Patients were consented in collaboration with the recruiting site and then contacted annually, if appropriate, directly by the trial centre.
- We calculated the proportion of eligible patients whose status could be ascertained, contacted, consented and provided follow up information via direct patient contact and/or NHS Digital data. We estimated the additional years of follow up and its cost.

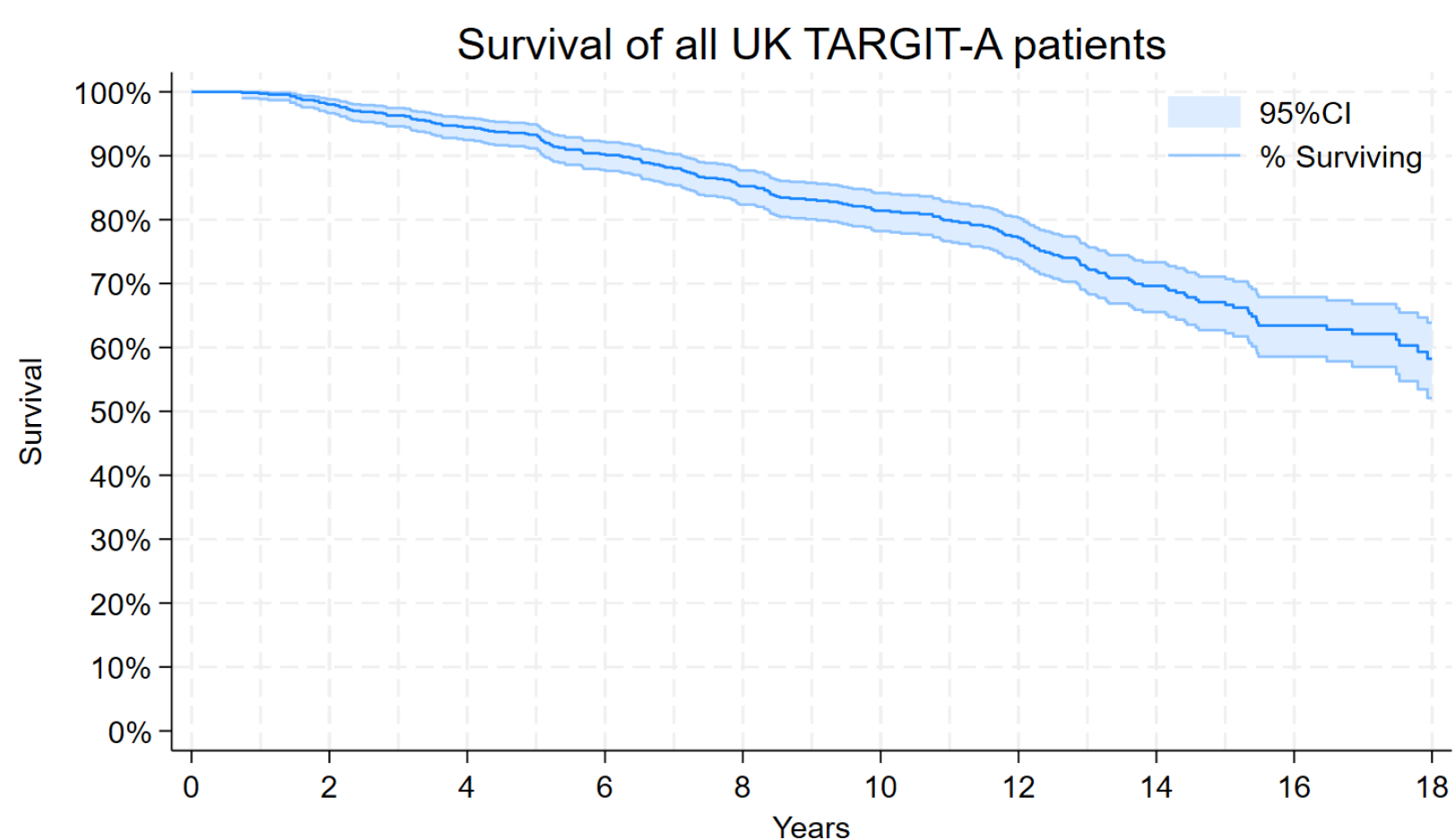
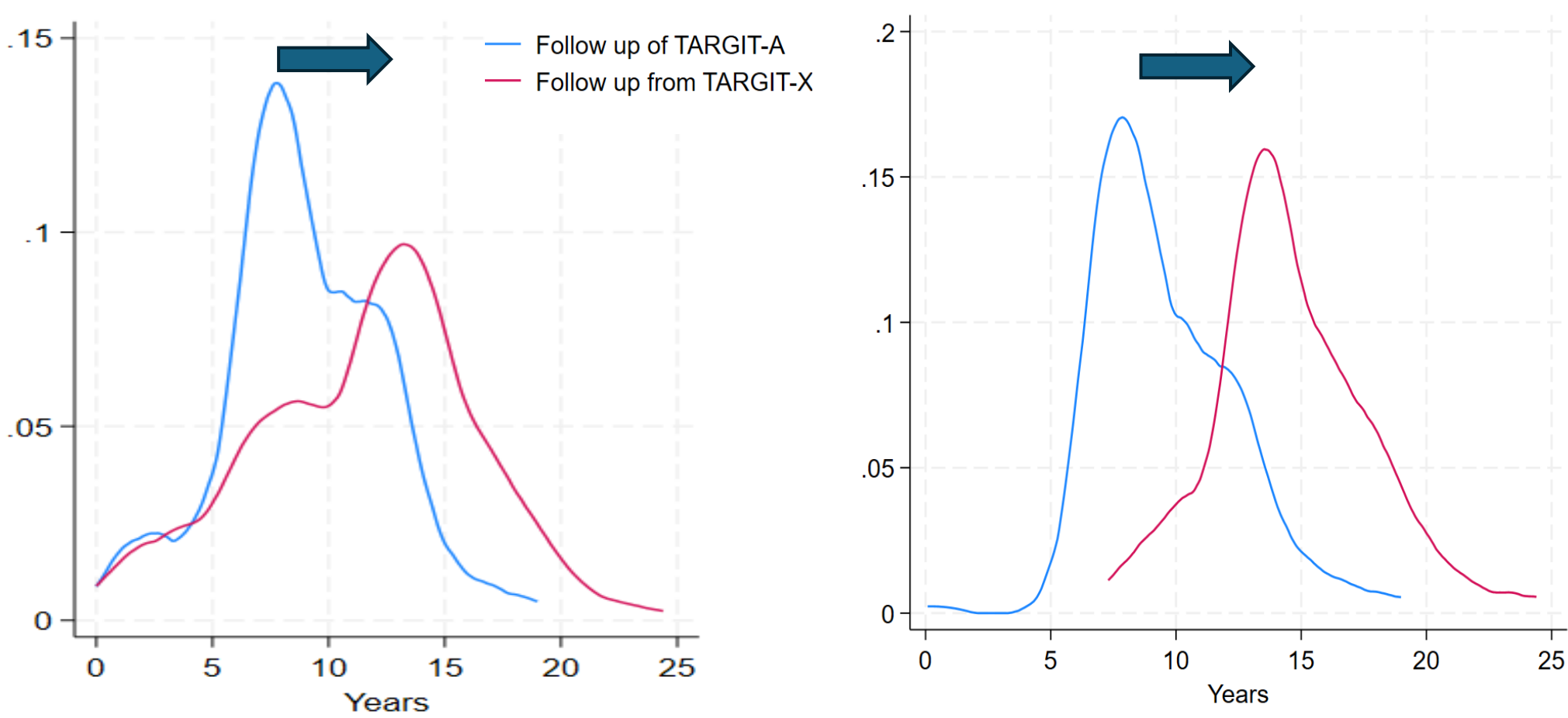
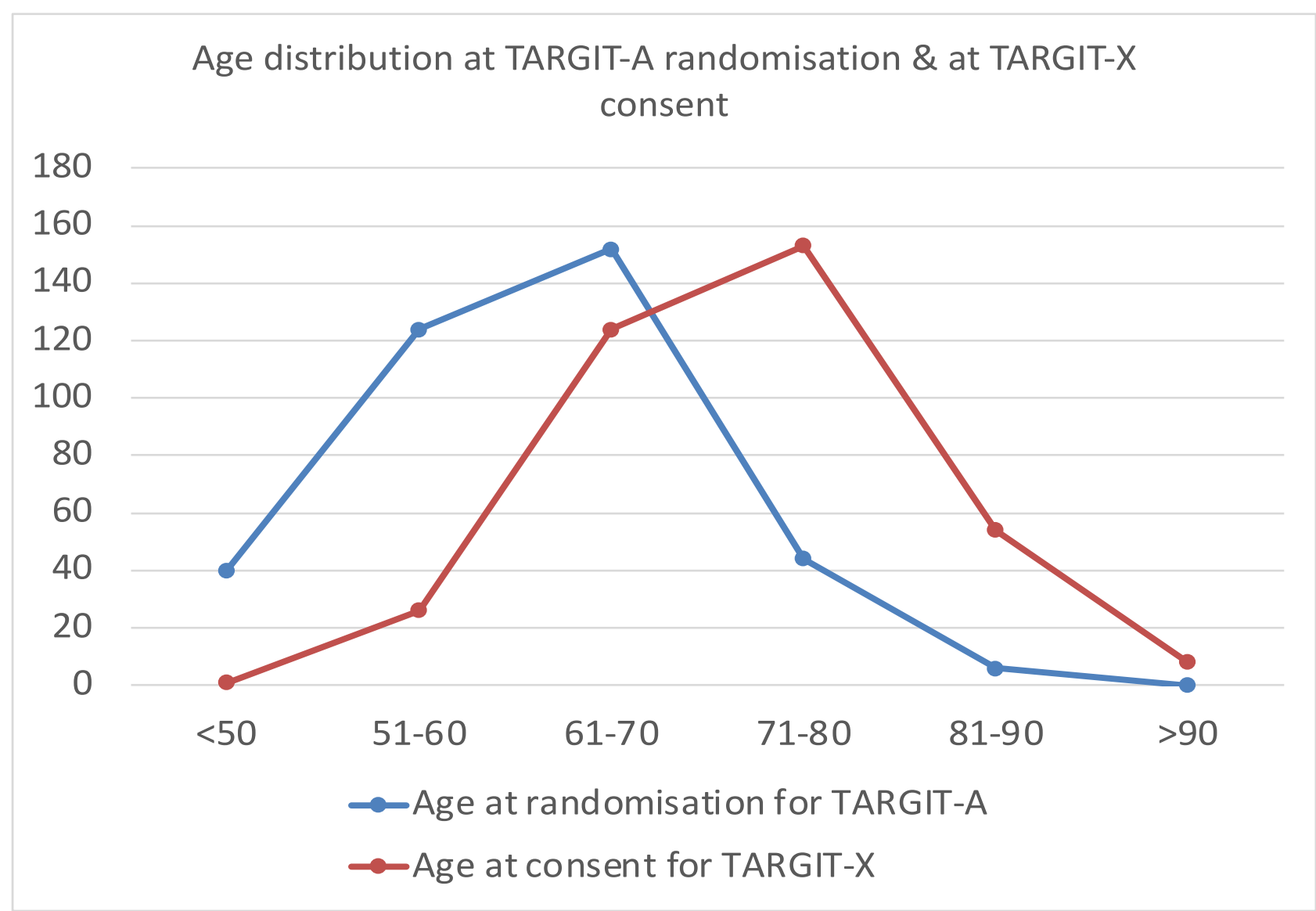
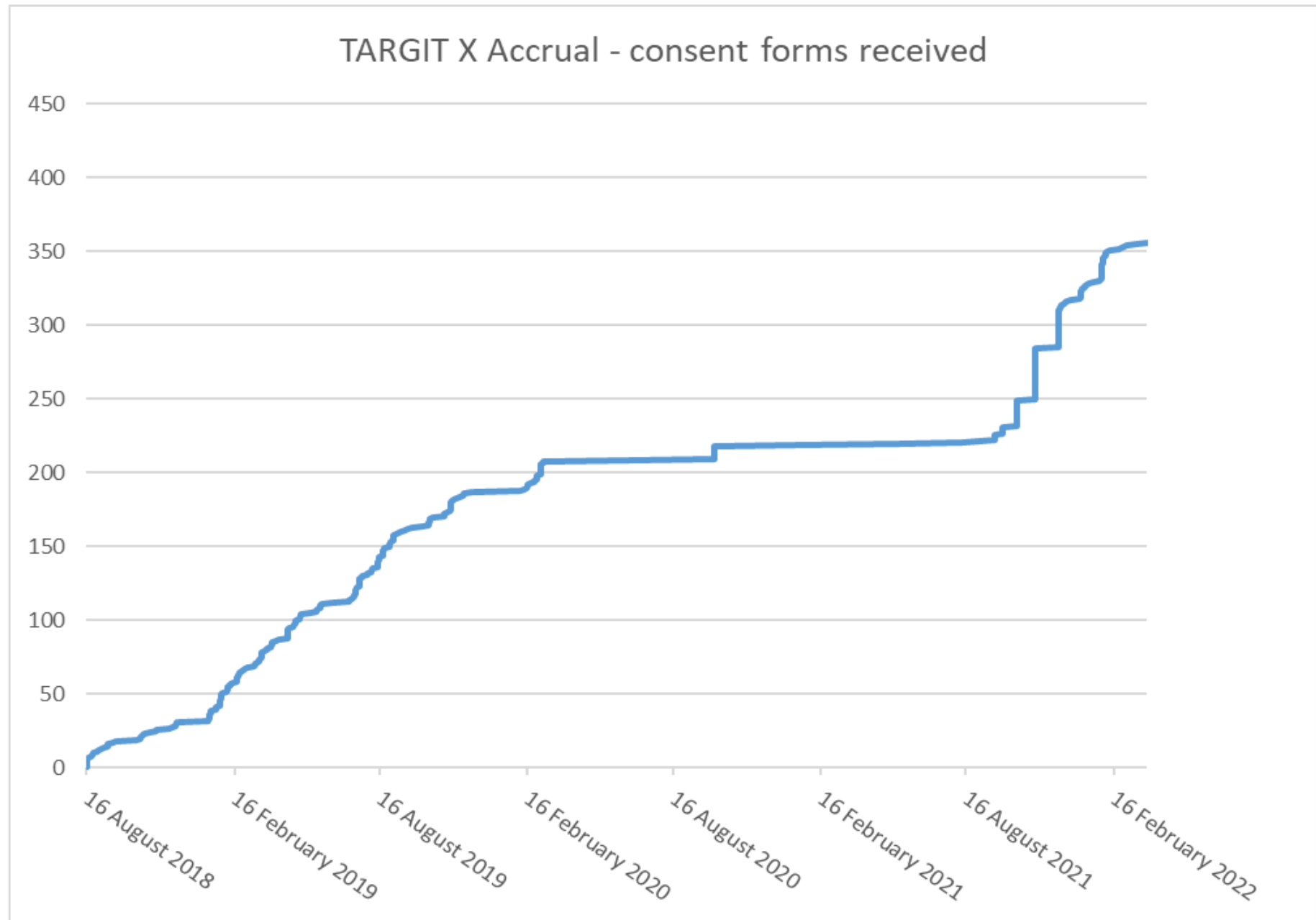
Results:

- 607 of 714 UK patients originally recruited in the TARGIT-A trials were initially eligible (dead/withdrawn not eligible).
- Of these, 94.5% (574/607) status / reason for non-participation was ascertained.
- Of these, 87% (502/574) patients' health status could be determined.
- Of these, 73% (366/502) or 60.3% of the total (366/607) were found to be in good health, provided valid consent for TARGIT-X and their health status.
- **Less than 5%(25/502) patients were unwilling to participate: 23 declined and 2 withdrew.**
- An additional 103 deaths recorded: doubling the initial number to 203.
- **A 65% overall survival at 15 years shows that unlike other PBI trials, TARGIT-A was NOT a low-risk cohort**
- The quality of data returned by patients was very good (e.g., mismatch rate for recording date <0.1%(1/1470 forms).
- **Patients who participated increased their follow up by a median 6 years (to 14 years (IQR 13 to 16)).**
- **The cost, including research funds, was < £60/patient/year of follow up.**
- Limitations included difficulties in receiving data from NHS Digital due to their due to repeated organisational changes, plus unexpected price rises in the costing of data download.

Recommendations for future research: To investigate why treatments proven in large international randomised trials showing patient benefit and are cost-effective, are not widely adopted in the UK whilst they are included in almost every other country's clinical practice guideline and widely adopted worldwide, to assess the influence of preconceived notions, conflicts of interest, and improve NICE processes.

Conclusion:

- In the UK, 95% patients are willing to be followed up long-term.
- It is feasible to collect follow up data for long-term health conditions accurately from patients with direct patient contact together with NHS Digital.
- It leads to a substantial increase in the length of follow up and number of relevant events, at a low cost.
- Our new approach could be adopted as an efficient method of obtaining long-term follow up data from patients in randomised clinical trials.



Introduction: We propose that the standard method of representing results of breast cancer radiotherapy clinical trials did not accurately represents what actually happens to patients: crucial for making treatment decisions.

Methods: While trying to present cumulative incidence rates of local recurrence (Kaplan-Meier plots) censoring- using patients’ length of follow up until they had last been seen alive– is included in the statistical model. Censoring should be non-informative, balanced, and censored patients must continue to have a risk of a local recurrence. We submit that if deaths are censored, the same statistical value is given to those-who-have-died and those-who-are-alive-with-shorter-follow-up-than-others, and it leads to misleading estimates and graphs.

Results: We illustrate this point with six examples of reputed trials with erroneous graphs: e.g. 60% of patients were alive at 10 years, so those alive without a local recurrence should inevitably be lower than 60%, yet their graph shows that 90% are alive without local recurrence. In contrast, local-recurrence-free survival (i.e. both death and local recurrence are events) truly represents what really happens to patients in terms of local control and effectiveness of treatment comprehensively, particularly when the treatments affect local disease and survival. It also follows the recommendations of ICH-GCP, European (DATECAN) and American (STEEP) guidelines.

Conclusion: The outcome of trials assessing local treatments such as radiotherapy for breast cancer, should be local recurrence-free survival, in which both local recurrence and deaths are events: it accurately reflects the expected outcomes, and should be used for shared decision-making with patients.

Cumulative local recurrence rate is a misleading and non-representative outcome

Example 1

The left-hand graph shows that only 60% are alive at 10 years. This being the case, how can 90% be alive without local failure as per the right-hand graph?

Self-contradictory

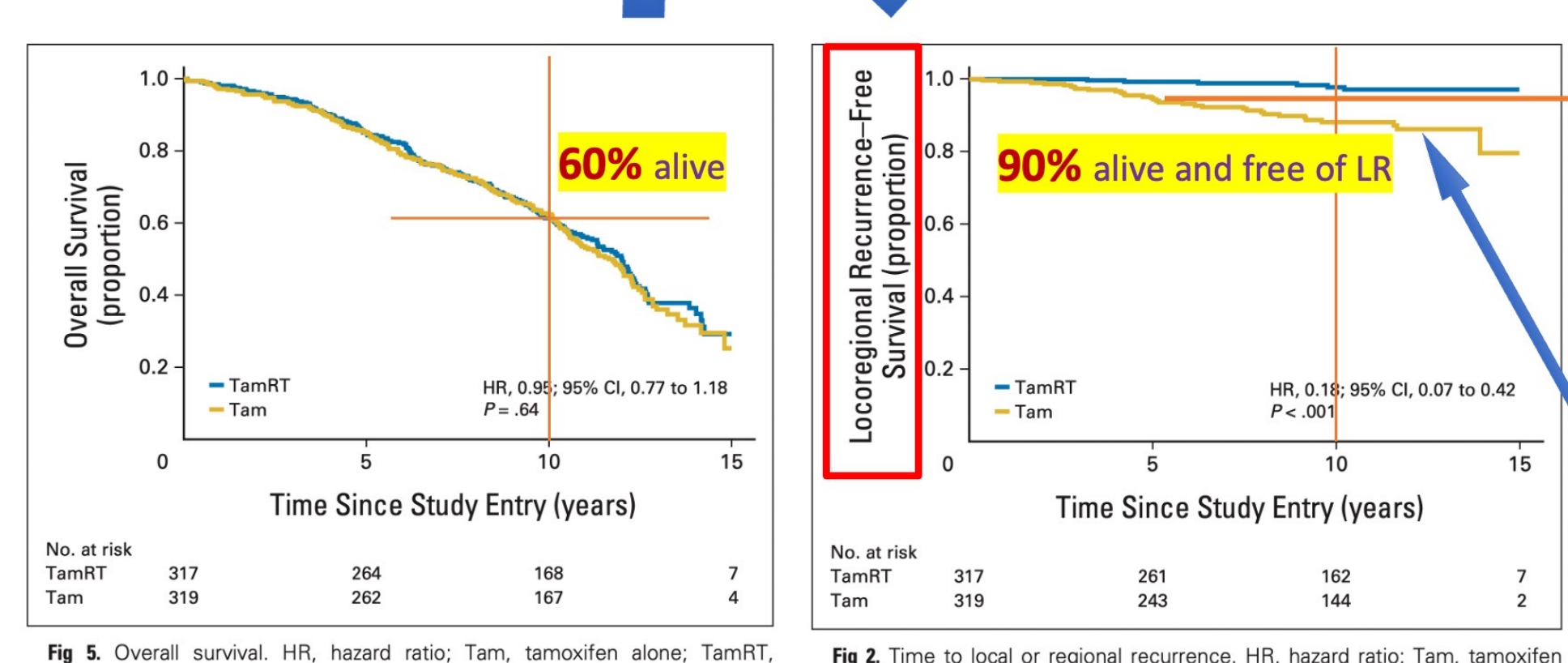


Fig 1. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

Fig 2. Time to local or regional recurrence. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

If only 60% are alive, how can >90% be alive without local recurrence (90% local recurrence free survival)?

So this right-hand graph labelled 'local recurrence free survival' is inaccurate and misleading for both patients and physicians. When the chance of being alive is only 60%, it is simply wrong to say that "You have a 90% chance of surviving without local recurrence"

Cumulative local recurrence rate is a misleading and non-representative outcome

Example 2

The left hand graph shows that only 80% are alive at 10 years. This being the case, how can 90% be alive without local failure as per the right-hand graph?

Self-contradictory

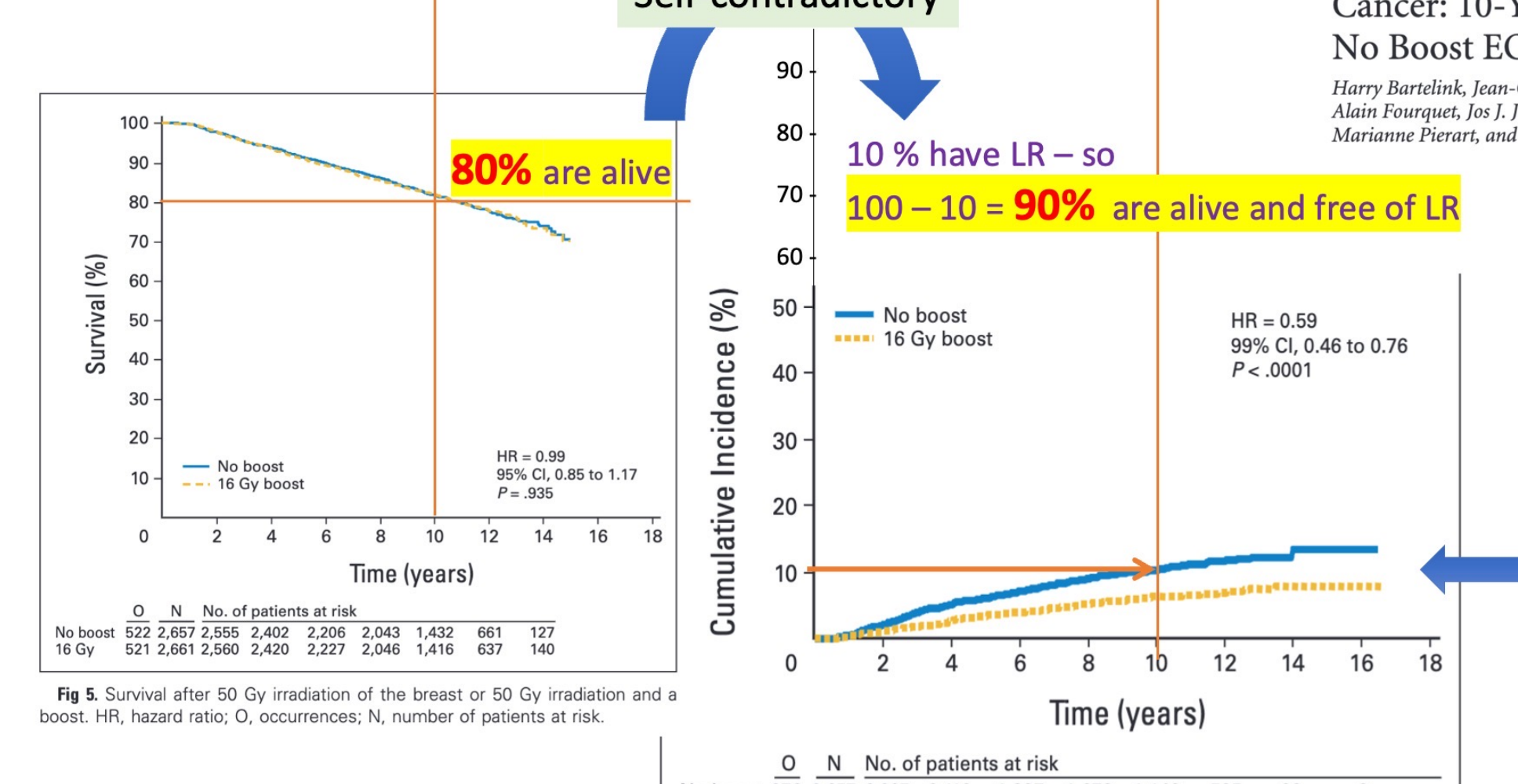


Fig 1. Survival after 50 Gy irradiation of the breast or 50 Gy irradiation and a boost. HR, hazard ratio; O, occurrences; N, number of patients at risk.

Fig 2. Cumulative incidence of recurrence of tumor as first event in the ipsilateral breast after 50 Gy whole-breast irradiation or 50 Gy whole-breast irradiation and a boost of 16 Gy. HR, hazard ratio; O, occurrences; N, number of patients at risk.

If only 80% are alive, how can >90% be alive without local recurrence?

So this right-hand graph is misleading for both patients and physicians.

Cumulative local recurrence rate is a misleading and non-representative outcome

Example 3

The left-hand graph shows that only 52% are alive at 10 years. This being the case, how can 86% be alive without local failure as per the right-hand graph?

Self-contradictory

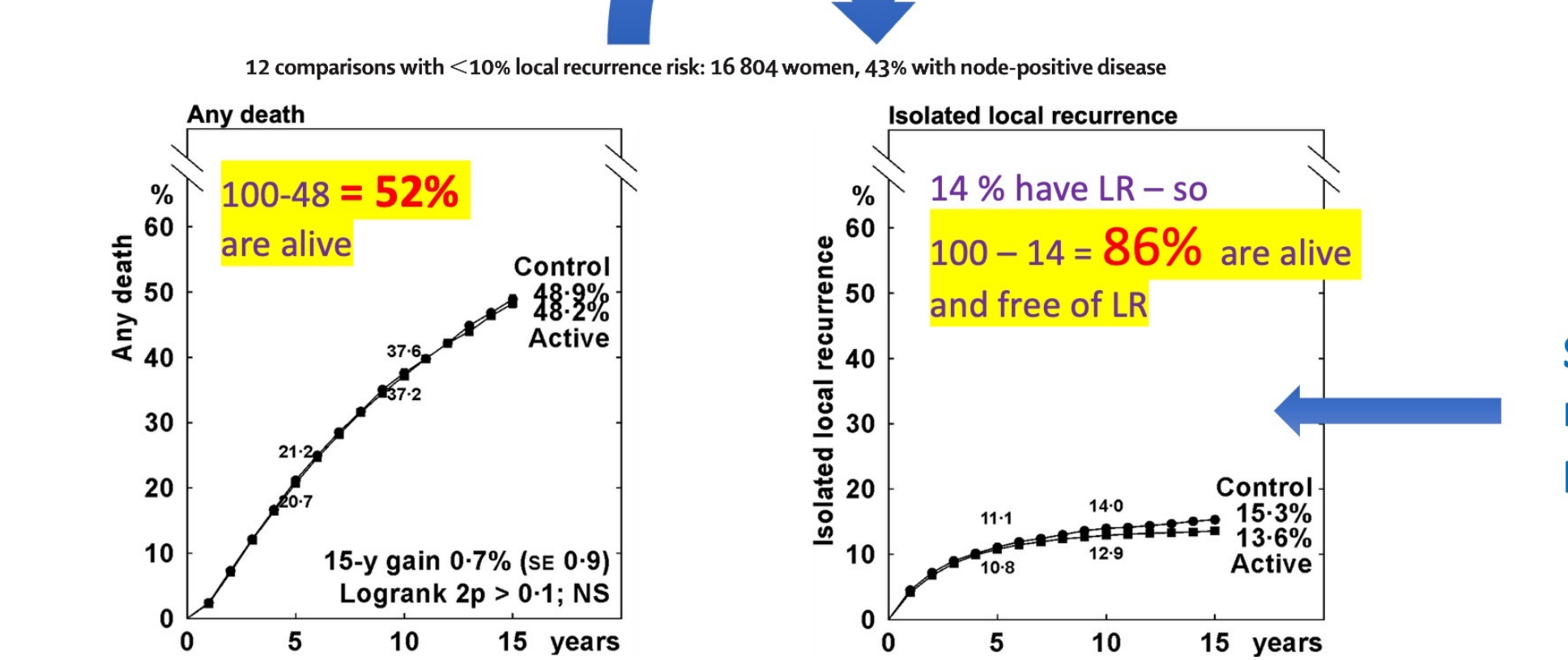


Fig 1. Any death. Logrank 2p > 0.1; NS.

Fig 2. Isolated local recurrence. Control 15.3% Active 15.9%.

If only 52% are alive, how can >86% be alive without local recurrence?

So this right-hand graph is misleading for both patients and physicians.

Cumulative local recurrence rate is a misleading and non-representative outcome

Example 4

The left hand graph shows that only 91% are alive at 10 years. This being the case, how can 95% to 96% be alive without local failure as per the right hand graph?

Self-contradictory

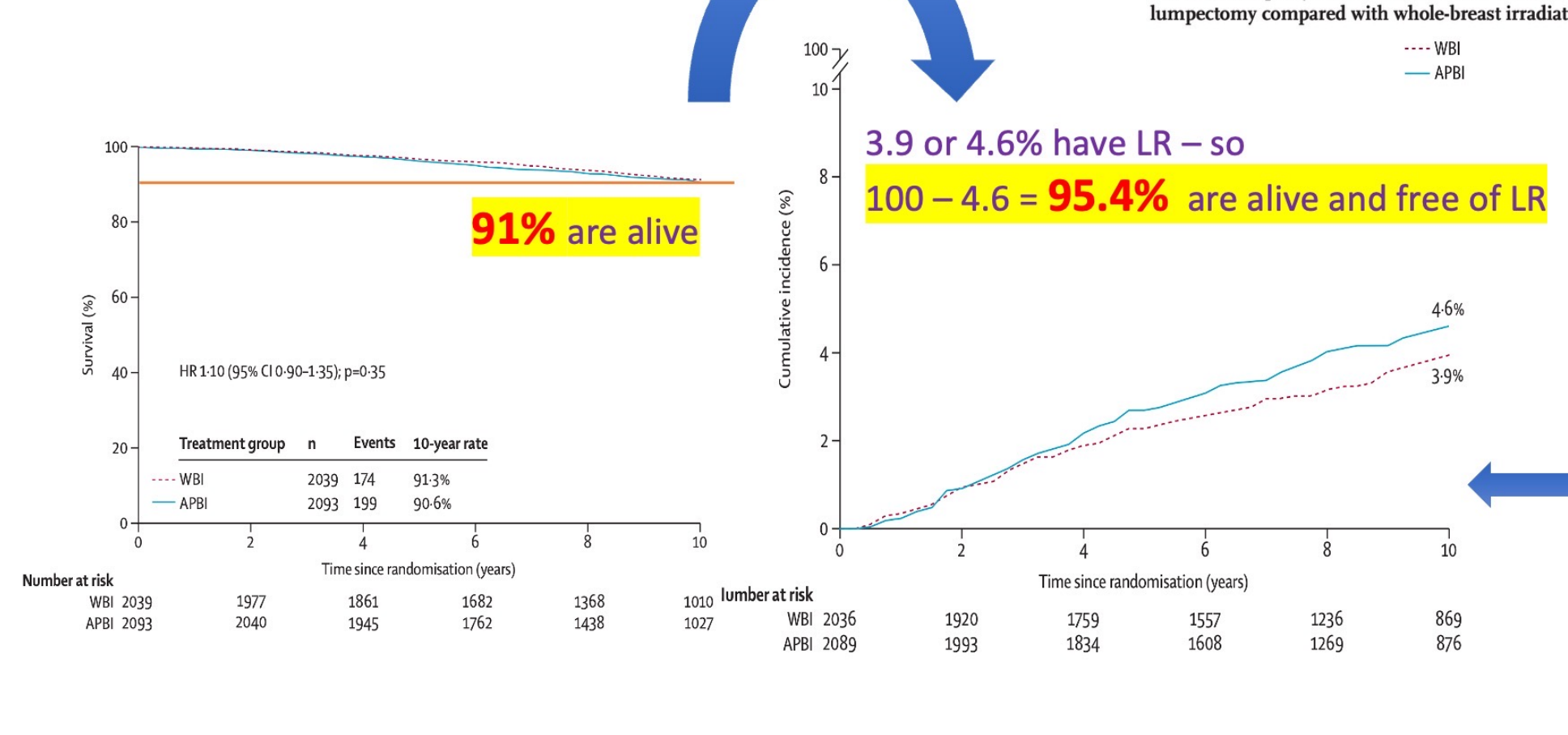


Fig 1. Survival. HR 1.0 (95% CI 0.94-1.05) p=0.35.

Fig 2. Cumulative incidence of local recurrence. WB 3.9% WB+RT 4.6%.

If only 91% are alive, how can >95% be alive without local recurrence?

So this right-hand graph is misleading for both patients and physicians.

Cumulative local recurrence rate is a misleading and non-representative outcome

Example 5

The left-hand graph shows that only 60% are alive at 10 years. This being the case, how can 90% be alive without local failure as per the right-hand graph?

Self-contradictory

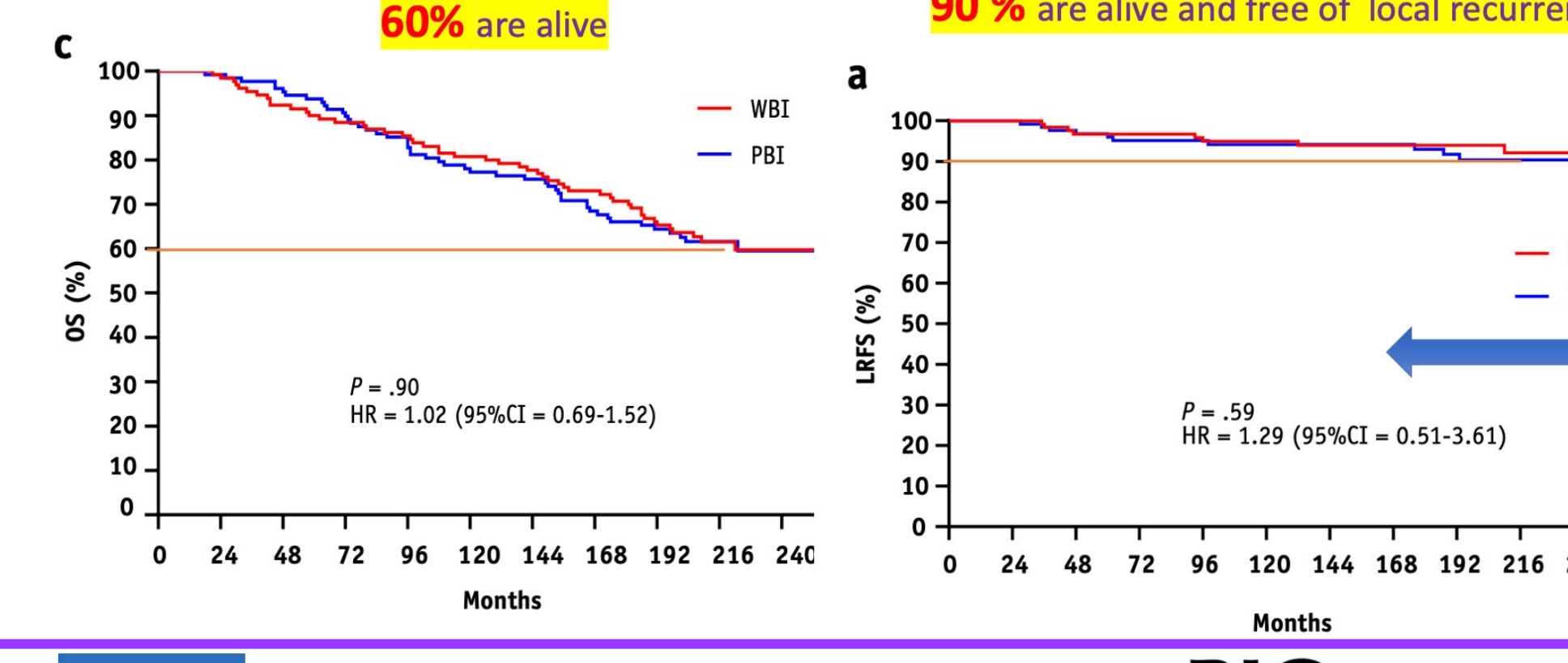


Fig 1. OS. P = .90 HR = 1.02 (95%CI = 0.69-1.52).

Fig 2. LRFS. P = .59 HR = 1.29 (95%CI = 0.51-3.61).

If only 60% are alive, how can 90% be alive and free of local recurrence?

So this right-hand graph is misleading for both patients and physicians.

Cumulative local recurrence rate is a misleading and non-representative outcome

Example 6

The left-hand graph shows that only 80% are alive at 10 years. This being the case, how can 90% to 99% be alive without local failure as per the right-hand graph?

Self-contradictory

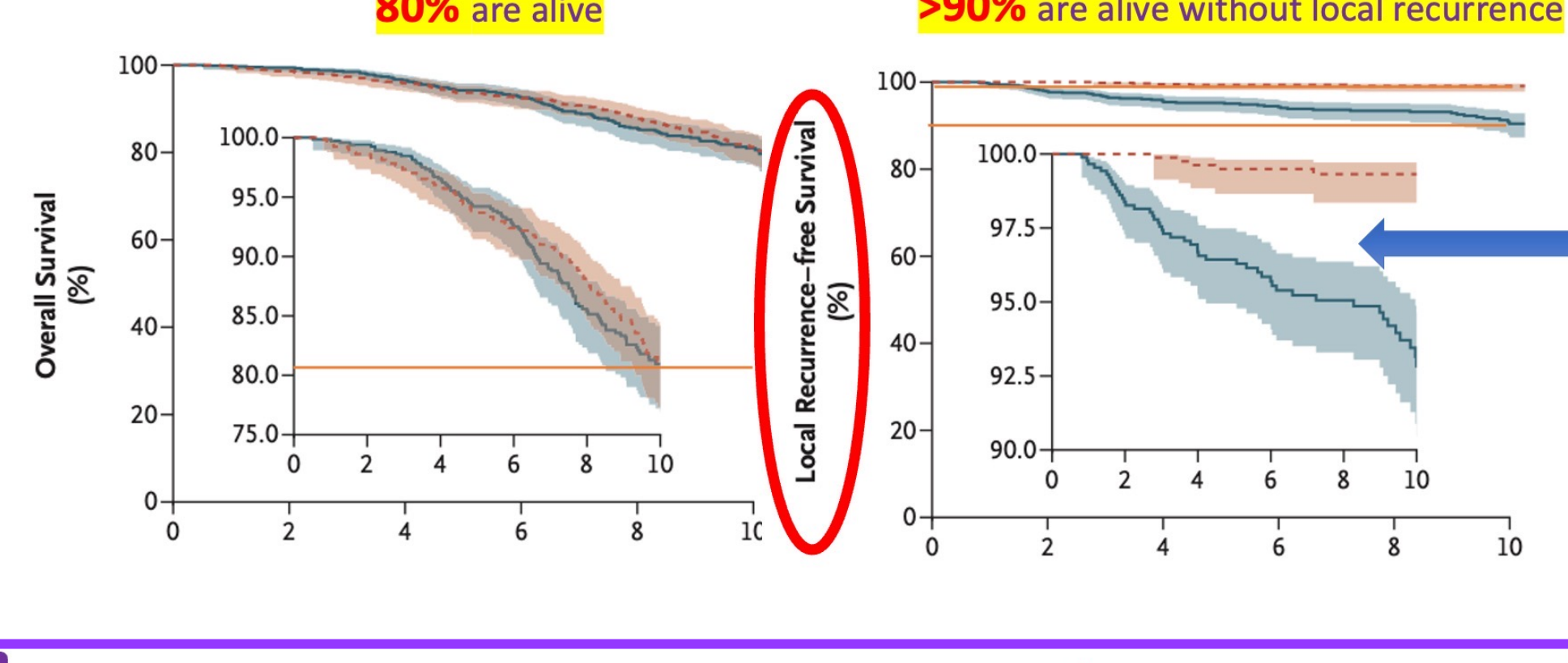


Fig 1. OS. P = .90 HR = 1.02 (95%CI = 0.69-1.52).

Fig 2. LRFS. P = .59 HR = 1.29 (95%CI = 0.51-3.61).

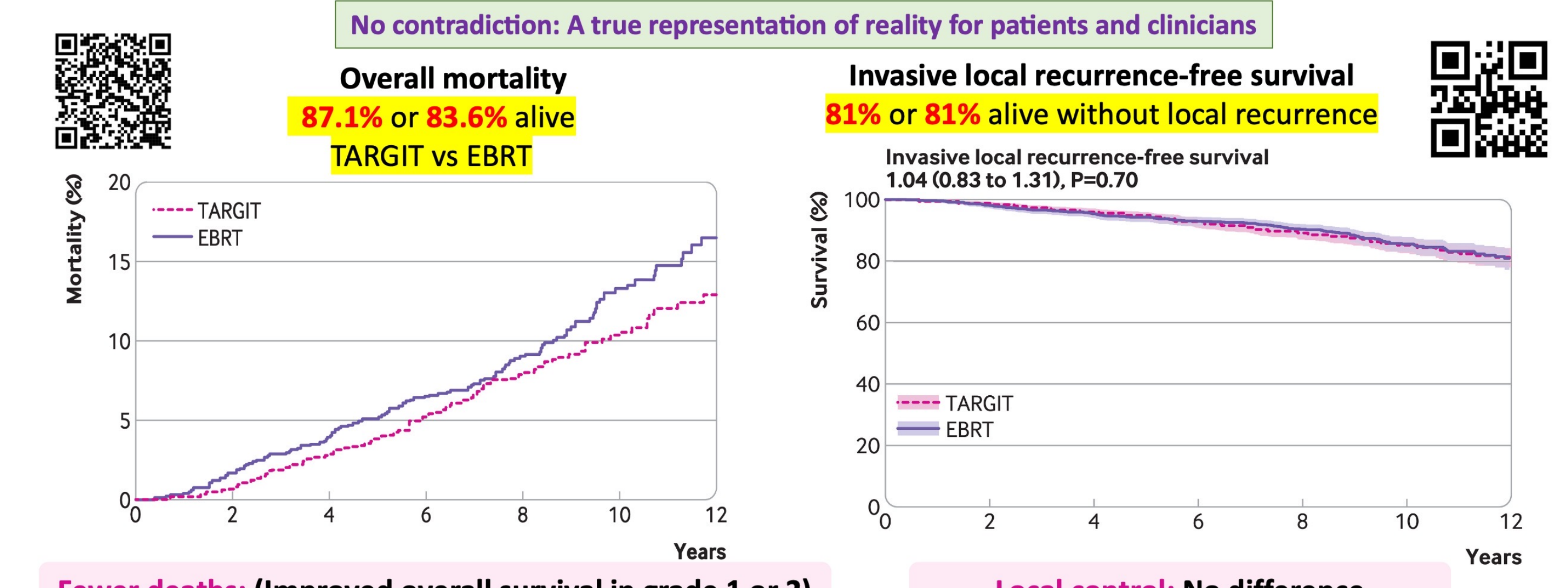
If only 80% are alive, how can 90.5% or 99.5% be alive and free of local recurrence?

So this right-hand graph is misleading for both patients and physicians. When the chance of being alive is only 80%, it is simply wrong to say that "You have a 90% or 99% chance of being (alive &) recurrence free"

The right way: Example 1

Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial

No contradiction: A true representation of reality for patients and clinicians



Overall mortality 87.1% or 83.6% alive TARGIT vs EBRT

Invasive local recurrence-free survival 81% or 81% alive without local recurrence

Fig 1. Mortality. P = .00042 HR = 0.47 (0.31-0.72).

Fig 2. Invasive local recurrence-free survival. P = 0.70 HR = 1.04 (0.83-1.31).

Fewer deaths: (Improved overall survival in grade 1 or 2)

Local control: No difference

The right way: Example 2

Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3-07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study

No contradiction: A true representation of reality for patients and clinicians

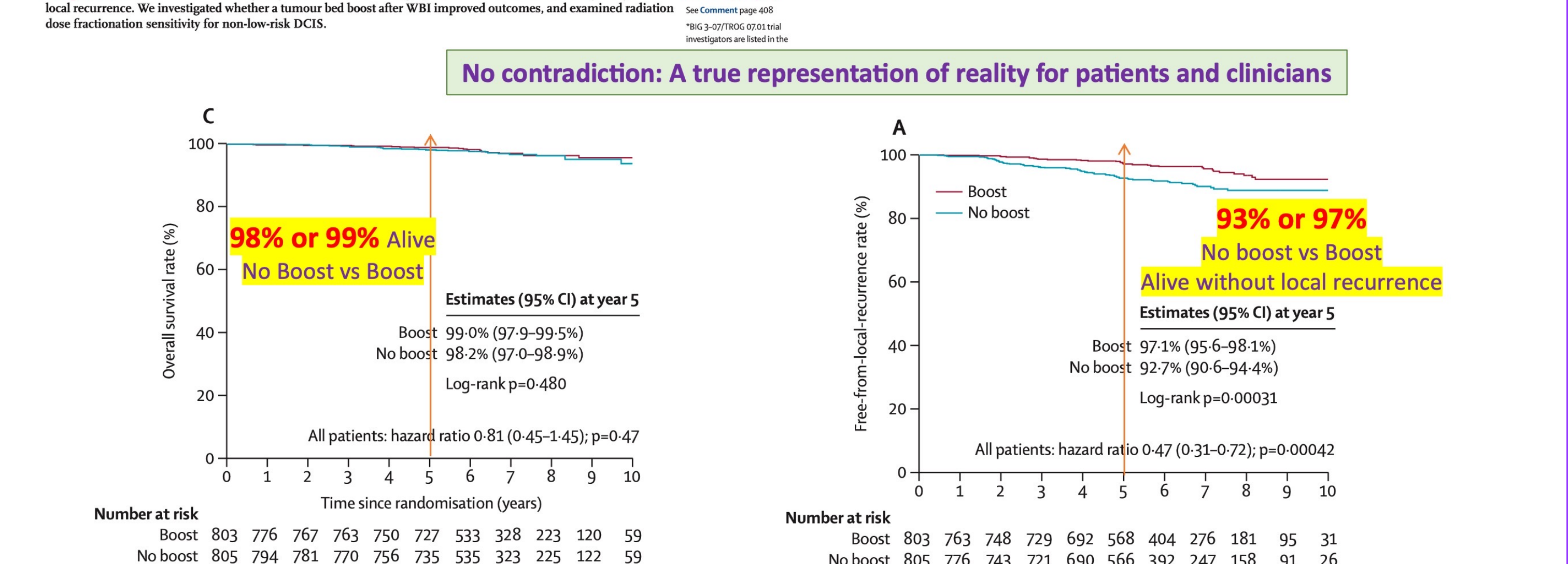


Fig 1. Overall survival rate. P = 0.480 HR = 0.81 (0.45-1.45).

Fig 2. Free-from-local-recurrence rate. P = 0.00042 HR = 0.47 (0.31-0.72).

98% or 99% Alive No Boost vs Boost

93% or 97% No boost vs Boost Alive without local recurrence