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Avoid systemic overtreatment of postmenopausal breast cancer patients with ultralow MammaPrint result

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Background

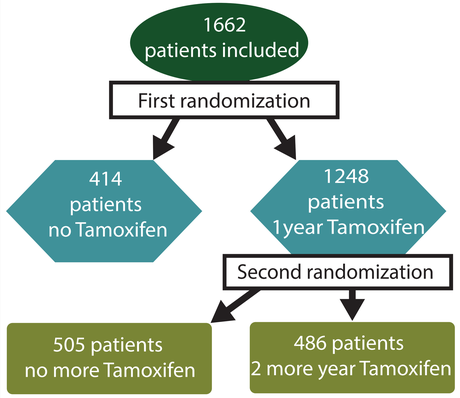
Adjuvant tamoxifen is widely used as endocrine treatment for oestrogen receptor positive (ER+) breast cancers (BC).
Guidelines recommend the use of tamoxifen up to 10 years.
Tamoxifen can cause serious side effects and not all patients need adjuvant tamoxifen to have an excellent prognosis.
To avoid overtreatment, a test that identifies these patients is necessary.

The 70-gene FDA-approved MammaPrint has potential to select patients that have an excellent survival without chemotherapy and only limited or no tamoxifen treatment.
Three thresholds are predefined and indicate the expected benefit of tamoxifen and chemotherapy.[1,2]

	Ultralow risk	Low risk	High risk
Endocrine	limited	Yes	Yes
Chemotherapy	NO	NO	Yes

Randomized controlled trial

Between 1982 and 1994, a total of 1662 postmenopausal patients with stage I to III BC were randomized for no, 1 or 3 years adjuvant tamoxifen treatment. [3]
After 1989 lymph node-positive patients always received at least 1 year of tamoxifen (30 mg/day).
All received surgery but no chemotherapy.



AIM: validate whether the MammaPrint ultralow threshold can select postmenopausal BC patients with an excellent prognosis after only limited or no tamoxifen treatment.

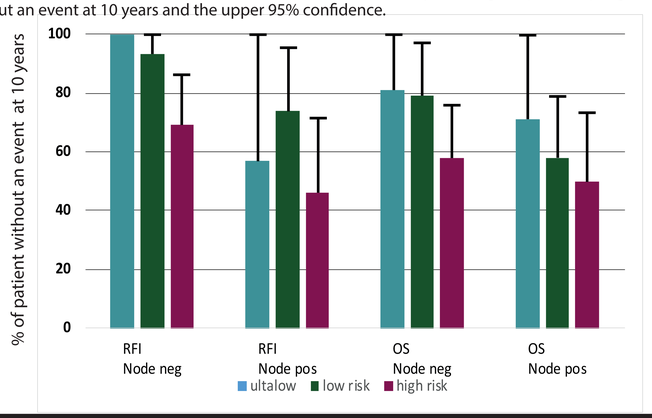
Patients

For 736 out of the 1662 patients we collected FFPE tumor material [4]. From the stored FFPE blocks, 482 were from ER+ HER2- stage I-III patients and of these 346 had sufficient material left for RNA isolation and MammaPrint test. This resulted in reliable scores for 135 patients. In the table below also the 347 ER+ HER2- stage I-III without a MammaPrint score are shown.

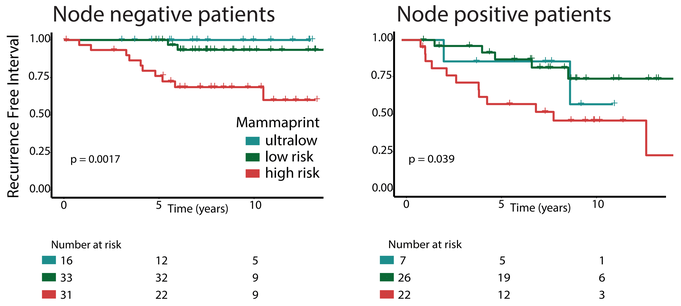
	Ultralow	Low risk	High risk	Not tested ER+HER2-
Number of patients	23	59	53	347
Age [<65 or >65 years]	52% 48%	47% 53%	55% 45%	47% 53%
Nodal status [neg or pos]	70% 30%	56% 44%	58% 42%	56% 44%
T-size [T1, T2 or T3]	17% 74% 9%	35% 58% 7%	22% 74% 4%	33% 59% 8%
Grade [I, II or III]	65% 35% 0	39% 37% 24%	13% 36% 51%	30% 40% 30%
Tamoxifen [0,1 or 3 years]	22% 43% 35%	22% 36% 42%	30% 42% 28%	24% 50% 26%

Survival analysis

Recurrence Free Interval (RFI) was defined as time from the first randomization to the occurrence of a local, regional or distant recurrence or breast cancer-specific death. Patients with a secondary contralateral breast tumor were censored at the time of the contralateral diagnosis. Median follow-up was 8 years for RFI and 13 year for overall survival (OS). Shown are the percentage of patients per group without an event at 10 years and the upper 95% confidence.

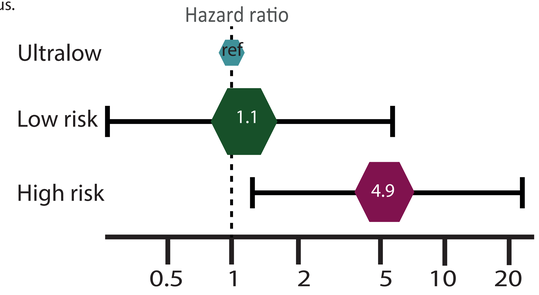


Kaplan Meier plots for Recurrence free interval



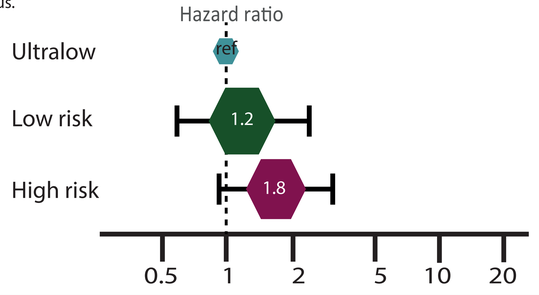
Cox proportional hazard model of Recurrence Free interval

stratfied for nodal status.



Cox proportional hazard model of Overall Survival

stratfied for nodal status.



CONCLUSION: Postmenopausal node negative patients with an Ultralow MammaPrint score have an excellent RFI with ≤3 years of endocrine treatment.

Discussion: Although the number of patients is small, this result is supported by the results of the STO-3 randomized clinical trial.[5] Clinicians should consider limiting endocrine treatment duration for this specific group of patients.

Future plan: Increase follow-up to 20 years to gain more evidence that patients with Ultralow MammaPrint results do not need long term endocrine treatment.

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Declaration of interest
Miranda Kleijn and Anuska Glas employed full-time by Agendia. All other authors declare no conflict of interest regarding this project.

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