

Surgery of the Primary Tumor in *De Novo* Metastatic Breast Cancer Patients is Associated with Increased Survival: a Nationwide Population-based Study by the Belgian Cancer Registry (BCR) and the Belgian Society of Medical Oncology (BSMO)

M. Brandão¹, C. De Angelis¹, P. Vuylsteke^{2,3}, R. Gelber⁴, N. Van Damme⁵, E. Van Eycken⁵, J. Verbeeck⁵, L. van Walle⁵, C. Colpaert⁶, M. Lambertini⁷, F. Poggio⁷, D. Verhoeven⁸, A. Barbeaux⁹, D. Duhoux¹⁰, K. Punie¹¹, H. Wildiers¹¹, C. Caballero¹², A. Awada¹³, M. Piccart¹³, E. de Azambuja^{1,13}

¹Academic Trials Promoting Team, Institut Jules Bordet, Brussels, Belgium, ²CHU UCL Namur, Site Ste Elisabeth, UC Louvain, Namur, Belgium, ³University of Botswana, Botswana ⁴Department of Data Sciences, Dana-Farber Cancer Institute, Harvard Medical School, Boston, United States of America, ⁵Belgian Cancer Registry, Brussels, Belgium, ⁶Pathology Department, UZ Leuven, Leuven, Belgium, ⁷IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy, ⁸Medical Oncology, AZ Klina, University of Antwerp, Antwerp, Belgium, ⁹Medical Oncology, CHR Verviers East Belgium, Verviers, Belgium, ¹⁰Department of Medical Oncology, Institut Roi Albert II, Cliniques universitaires Saint-Luc, Brussels, Belgium, ¹¹Medical Oncology, UZ Leuven, Leuven, Belgium, ¹²Breast International Group, Brussels, Belgium, ¹³Department of Oncological Medicine, Institut Jules Bordet, Brussels, Belgium

Background & Objectives

- In Western countries, about 5%-10% of patients with breast cancer (BC) have distant synchronous metastases at diagnosis (***de novo* stage IV disease**).^{1,2}
- Meta-analyses of retrospective observational studies **suggested a survival benefit from primary BC surgery**, especially in some specific subgroups of patients, such as women with estrogen receptor (ER)-positive or with low burden-disease.⁴⁻⁶
- Three **prospective randomized clinical trials** investigated the role of surgery of the primary tumor in patients with *de novo* metastatic BC,⁷⁻⁸ but reported **conflicting results**.
- The role of locoregional treatment such as **surgery** and/or radiotherapy of the primary breast tumor **still remains highly debatable** in this setting.³
- We aimed to assess **Overall Survival (OS)** among *de novo* metastatic BC patients who underwent Surgery of the primary tumor within 9 months after diagnosis vs patients who did not, **adjusting for prognostic factors**.

Methods

- Study design:** retrospective population-based study.
- Population:** **2,627 women** diagnosed with *de novo* metastatic BC from **2010-2014**, with data obtained from the Belgian Cancer Registry and linked with administrative health care databases, followed until **12-09-2019**.
- A **9-month landmark analysis** excluding patients who died/were lost to follow-up <9 months after diagnosis was performed.
- Baseline patients' characteristics and treatment received were compared between "Surgery" vs "No Surgery" groups using Chi² and t tests.
- OS was estimated using Kaplan-Meier method and compared using log-rank test and adjusted Cox proportional hazards models.
- Subgroup analysis for OS and a sensitivity analysis only including patients who received surgery as an upfront treatment were performed.
- All tests were two-sided and confidence intervals (CIs) were reported at the 95% level. P values < 0.05 were considered statistically significant.

Results

- 1,985 patients** were included in the 9-month landmark analysis, 534 in the "Surgery" and 1451 in the "No Surgery" group.
- Patients receiving Surgery were younger, had better performance status (PS) at diagnosis and higher rate of HER2+ subtype (**table 1**).
- Median follow-up: **86.0 months** (95% CI, 82.6-88.5).

- Median OS was **41.9 months** in the "No Surgery" group vs **60.1 months** in the "Surgery" group – **adjusted hazard ratio (HR)** for age, performance status (PS) at diagnosis, tumor subtype, T status and histological grade: **0.56** (95% CI, 0.49-0.64) – **figure 1**.

- Survival differences were larger in patients with PS 0-1, ER+/HER2- or HER2+ BC (**figures 1 & 2**).
- OS was **not better** among patients with PS 2-4, while absolute differences were small among patients with triple-negative BC.

- Sensitivity analysis showed similar results (**figure 3 & table 2**).

Patient and treatment characteristics

	No surgery n=1,451 (%)	Surgery n=534 (%)	p value
Age (in years)			
<50	219 (15.1)	119 (22.3)	<0.001
50-59	248 (17.1)	121 (22.7)	
60-69	328 (22.6)	126 (23.6)	
≥70	656 (45.2)	168 (31.5)	
Clinical T category			
T0/T1/T2	645 (49.9)	272 (51.8)	0.457
T3/T4	648 (50.1)	253 (48.2)	
Missing	158	9	
Clinical N category			
N0	308 (25.1)	144 (28.2)	0.186
N+	918 (74.9)	367 (71.8)	
Missing	225	23	
Histological grade			
G1/2	724 (59.6)	234 (46.8)	<0.001
G3	491 (40.4)	266 (53.2)	
Missing	236	34	
WHO PS at diagnosis			
0	345 (25.6)	197 (39.4)	<0.001
1	877 (65.0)	272 (54.4)	
2	91 (6.8)	24 (4.8)	
3/4	36 (2.7)	7 (1.4)	
Missing	102	34	
Tumour subtype			
ER+/HER2-	1,066 (73.5)	357 (66.9)	0.013
ER+/HER2+	179 (12.3)	88 (16.5)	
ER-/HER2+	110 (7.6)	40 (7.5)	
TNBC	96 (6.6)	49 (9.2)	
Histology			
Ductal	1,076 (74.2)	417 (78.1)	0.152
Lobular	242 (16.7)	71 (13.3)	
Others	133 (9.2)	46 (8.6)	
Type of first-line therapy			
Surgery	0	241 (45.1)	<0.001
Chemotherapy (± trastuzumab)	568 (39.2)	239 (44.8)	
ET(± trastuzumab)	881 (60.7)	54 (10.1)	
Trastuzumab only	2 (0.1)	0	
Type of systemic first-line therapy			
Chemotherapy	342 (23.6)	237 (44.4)	<0.001
Chemotherapy + trastuzumab	226 (15.6)	91 (17.0)	
Endocrine therapy (ET)	835 (57.6)	198 (37.1)	
Endocrine therapy + trastuzumab	46 (3.2)	8 (1.5)	
Trastuzumab only	2 (0.1)	0	
Radiotherapy (any site)	430 (29.6)	351 (65.7)	<0.001
Type of surgery			
Breast conservative surgery	NA	157 (29.4)	NA
Mastectomy	NA	377 (70.6)	
Timing of breast surgery			
<90 days	NA	252 (47.2)	NA
90-179 days	NA	123 (23.0)	
≥180 days	NA	159 (29.8)	
Region of treatment			
Brussels	115 (7.9)	111 (20.8)	<0.001
Flanders	1,022 (70.4)	259 (48.5)	
Wallonia	314 (21.6)	164 (30.7)	
Type of breast cancer center			
< 125 new cases/year	284 (19.6)	106 (19.9)	0.890
≥ 125 new cases/year	1,167 (80.4)	428 (80.2)	

Table 1: Patient and treatment characteristics of the "Surgery" vs "No Surgery" group. ER: estrogen receptor; NA: not applicable; PS: performance status; TNBC: triple negative breast cancer. Note: data on the number of metastatic sites per patient was not available

Overall survival in the "Surgery" vs "No Surgery" group

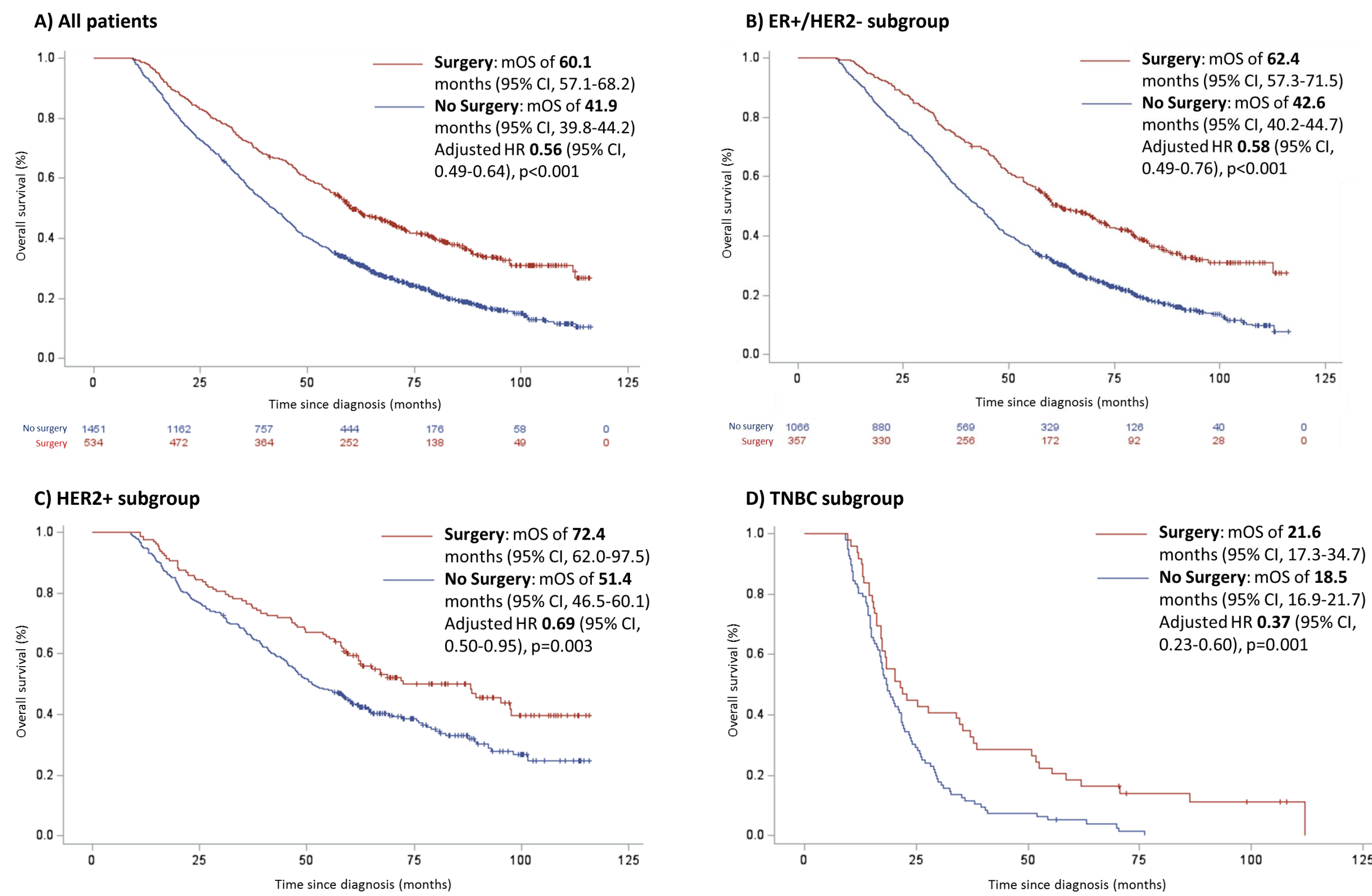


Fig.1 : Kaplan-Meier curves for overall survival in A) all patients, B) patients with estrogen receptor (ER)-positive/HER2- tumors, C) HER2-positive and D) triple-negative breast cancer (TNBC). CI: confidence interval; HR: hazard ratio – adjusted for age, performance status at diagnosis, tumor subtype, T category and histological grade.

Sensitivity analysis: "Upfront Surgery" vs "Surgery after systemic treatment" vs "No Surgery"

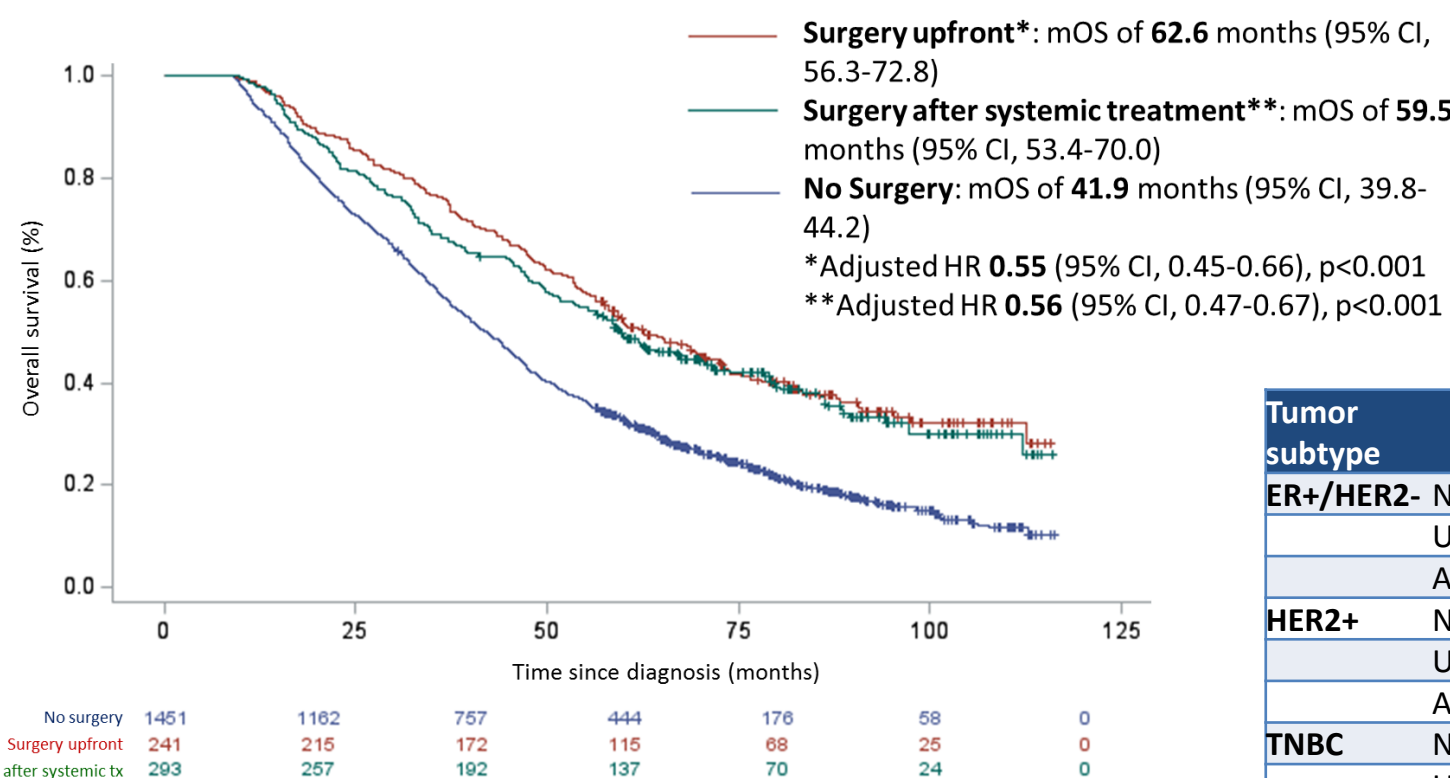


Fig.3: Kaplan-Meier curves for overall survival (OS) in patients receiving surgery as upfront treatment vs surgery after systemic treatment vs no surgery

Table 2: Multivariable analysis of OS in the "Upfront Surgery (Sx)" vs "Surgery after systemic treatment (tx)" vs "No Surgery" within each subgroup of patients according to tumor subtype.

Tumor subtype	N	Median OS (95% CI)	p value	Adjusted HR (95% CI)
ER+/HER2- No Surgery	1066	42.6 (40.2-44.7)		1
Upfront Sx	184	62.6 (56.3-73.2)	<0.001	0.55 (0.44-0.68)
After syst tx	173	62.4 (51.8-79.0)	<0.001	0.61 (0.49-0.76)
HER2+ No Surgery	289	51.4 (46.5-60.1)		1
Upfront Sx	45	72.4 (54.6-NR)	0.069	0.82 (0.51-1.31)
After syst tx	83	88.5 (59.2-NR)	0.008	0.63 (0.42-0.93)
TNBC No Surgery	96	18.5 (16.9-21.7)		1
Upfront Sx	12	20.7 (12.9-52.6)	0.049	0.45 (0.20-0.99)
After syst tx	37	21.6 (17.2-37.2)	0.004	0.35 (0.20-0.61)

Subgroup analysis of OS according to "Surgery" vs "No Surgery"

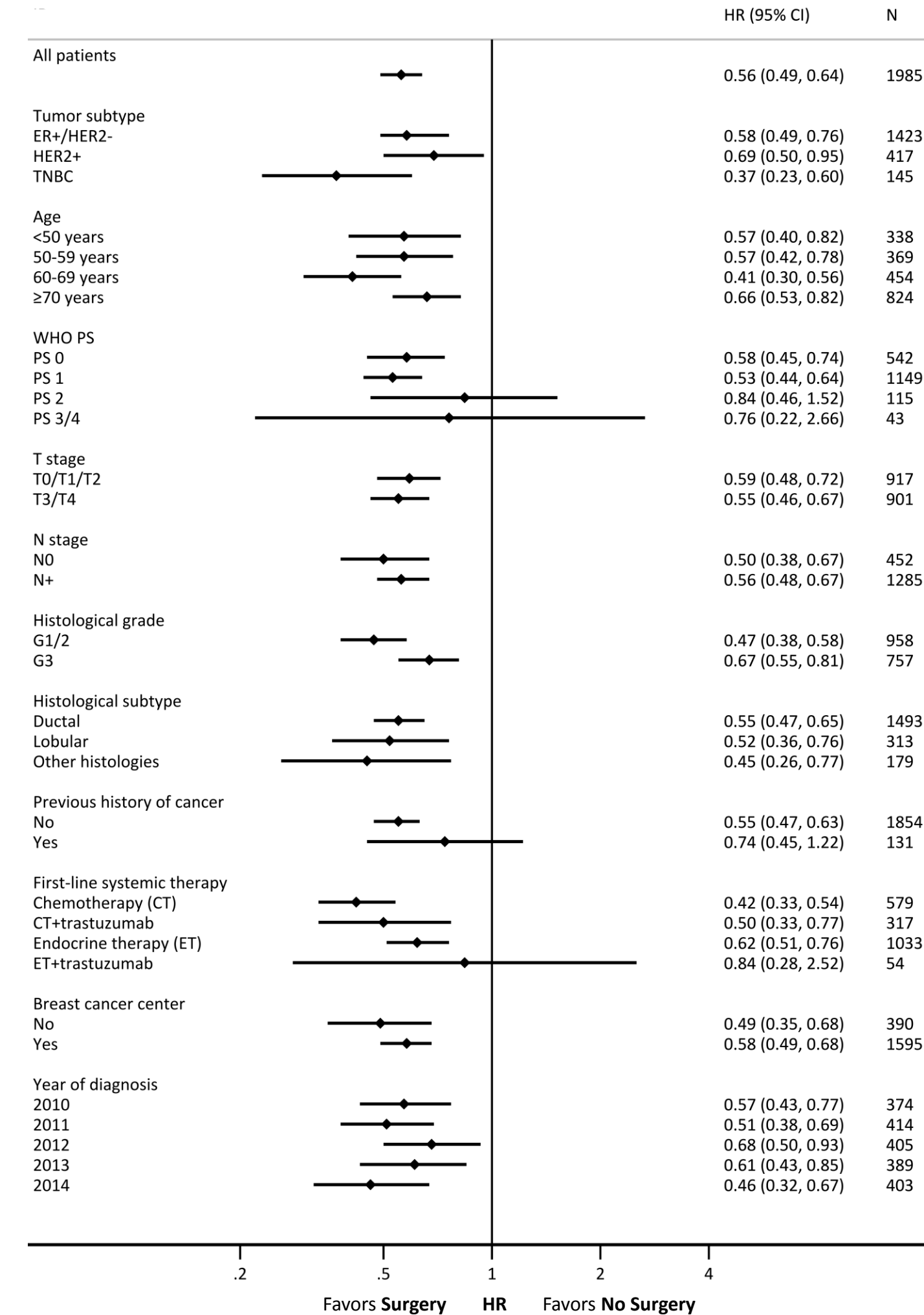


Fig.2 : Multivariable* analysis of overall survival according to "Surgery" vs "No Surgery" within each subgroup of patients. * All models included the variables: age, performance status (PS) at diagnosis, tumor subtype, T category and histological grade. CI: confidence interval; ER: estrogen receptor; HR: hazard ratio; TNBC: triple-negative breast cancer.

Conclusions

- Among *de novo* metastatic breast cancer patients **surviving ≥9 months after diagnosis**, those receiving surgery have **longer subsequent survival** compared to those who did not undergo surgery within 9 months of diagnosis.
- Survival differences were more pronounced among patients with **good performance status (0/1)** and with **ER+/HER2- and HER2+ BC**.
- Surgery of the primary tumor may thus be discussed as a **potential therapeutic intervention** to selected breast cancer patients.

Disclosures

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