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Clinicopathological Features, Treatment Patterns, and Survival Outcomes in Male Breast Cancer: A Multicenter Retrospective Analysis from the Czech Republic (2007–2017)

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Abstract

Male breast cancer (MBC) represents an uncommon yet rising malignancy that suffers from a scarcity of prospective research. International cooperation is essential to better comprehend and manage MBC, particularly its prognostic aspects, across various nations. A retrospective analysis was conducted on the clinical, histopathological, and molecular-genetic features, therapeutic approaches, and survival results for cases of MBC identified from 2007 to 2017 within the Czech Republic. Factors influencing overall survival (OS), recurrence-free interval (RFi), and breast cancer-specific mortality (BCSM) were assessed and informally benchmarked against global datasets. The cohort included 256 individuals diagnosed with MBC (median age 66 years), among whom 12% presented with de novo metastatic disease (M1). Among the 201 non-metastatic (M0) cases, 6% were younger than 40 years, 29% were classified as stage I, 55% were clinically node-negative (cN0), and 54% received genetic evaluation. In total, 97% of tumors showed estrogen receptor positivity of ≥10%, 61% exhibited elevated Ki67 levels, 40% were graded as high (G3), and 68% corresponded to luminal B-like subtype (HER2-negative). Systemic treatments comprised endocrine therapy in 90% and chemotherapy in 53%. Only 5% of patients stopped adjuvant endocrine therapy for causes unrelated to progression or mortality. Those receiving aromatase inhibitors monotherapy demonstrated markedly reduced RFi ($P < .001$). Associations with OS, RFi, and BCSM included tumor stage, T category, N category, progesterone receptor status, histological grade, and Ki67 proliferation index. Median OS was 122 months for M0 patients and 42 months for those with de novo M1 disease. Given the infrequent occurrence of MBC, this investigation provides valuable insights derived from routine clinical settings. Despite a greater proportion of adverse characteristics in this Czech population relative to published international cohorts, outcomes aligned closely with existing real-world observations.

Keywords: Male breast cancer, Epidemiology, Genetic testing, Prognosis, Retrospective study

Introduction

Breast cancer (BC) ranks as one of the most common malignancies in women (female breast cancer, FBC), whereas its occurrence in men (male breast cancer, MBC) remains exceptionally infrequent. Nevertheless, MBC rates have shown an upward trend in recent decades [1-3]. Patterns in the Czech Republic mirror global trends. The incidence stood at 1.33 per 100 000 during 2016-2020, reflecting a 6.4% rise compared to 2011-2015, and has doubled since the early 1990s (0.7 per 100 000 in 1991-1995; **Table 1**). Over the study interval (2007-2017), around 580 MBC diagnoses were recorded, equating to roughly 45-65 new cases annually. Similar to other uncommon conditions, MBC carries a relatively unfavorable outlook, particularly when contrasted with FBC, even as more breast cancer trials now include male participants [4, 5].

MBC generally demonstrates high endocrine responsiveness [5-8], tends to arise in central breast locations [5], primarily impacts elderly men [9], and is often detected at later stages [5] than FBC. BRCA2

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alterations represent the predominant genetic drivers of inherited MBC [10].

Management of MBC is largely adapted from protocols established for FBC [11]. Adjuvant chemotherapy (CT) schedules for MBC mirror those applied in FBC. Regarding adjuvant endocrine therapy (ET), patients unable to tolerate tamoxifen (TMX)—the preferred agent—may receive an aromatase inhibitor (AI) plus a luteinizing hormone-releasing hormone (LHRH) agonist [12]. Current international recommendations advocate genetic counseling and testing for every MBC patient [11-14].

Coordinated specialist care could enhance outcomes for MBC and similar rare entities. In the Czech Republic, Complex Oncological Centers (COCs) facilitate access to novel targeted agents and investigational trials. This research sought to characterize patient profiles, disease features, therapeutic patterns, and survival in MBC cases managed through Czech COCs, while performing informal comparisons with published international series.

Materials and Methods

Study design and population

A retrospective review of data from individuals diagnosed with MBC between 2007 and 2017 was performed using records from participating institutions within the Complex Oncological Centers (COC) network. These data were subsequently consolidated, analyzed, and processed statistically at the Masaryk Memorial Cancer Institute in Brno, Czech Republic (MMCI). Enrollment occurred across 9 out of 15 COCs nationwide (3 located in Prague, and one each in Hradec Kralove, Liberec, Usti nad Labem, Plzen, Brno, and Zlin; **Figure 1**). Prior to initiating therapy, every patient provided written informed consent for the use of personal data in research purposes, as required by patient rights documentation. The research protocol received approval from the Institutional Ethical Committee at MMCI (protocol code 2023/825/MOU).

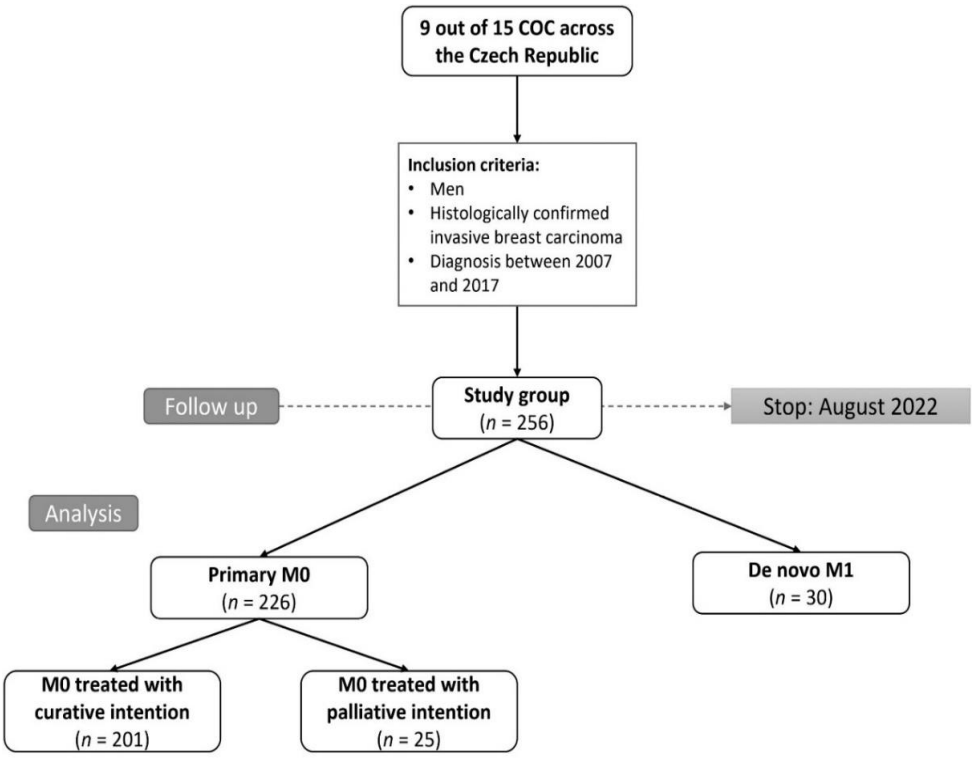


Figure 1. Study design.

The database contained anonymized information on diagnosis date and final follow-up or death, tumor stage, age at diagnosis, primary histopathological features of MBC (including histological subtype, grade [G], Ki67 proliferation index, expression of estrogen receptor [ER], progesterone receptor [PR], and human epidermal

growth factor receptor 2 [HER2]), surgical details and dates, radiotherapy (RT) modalities, genetic testing outcomes, and treatment specifics (including type of adjuvant/neoadjuvant therapy when applicable, and up to 3 lines of palliative therapy for metastatic or recurrent cases). The biopsy date served as the reference for the diagnosis year.

Complete histopathological reports were accessible for all included cases, incorporating routine immunohistochemical (IHC) assessments of ER, PR, and HER2, along with in situ hybridization for HER2 in samples showing equivocal (2+) IHC results. Staging relied on definitive pathological findings (pTNM), except in neoadjuvant-treated patients, where clinical staging (cTNM) was applied. Subtyping of MBC followed histopathological criteria: luminal A-like (ER-positive, PR > 10%, Ki67 < 15%); luminal B-like, HER2-negative (ER-positive, HER2-negative, PR < 10% or Ki67 > 20%); luminal B-like, HER2-positive (ER-positive, HER2-positive, any PR and Ki67); HER2-positive, non-luminal (ER-negative, PR-negative, HER2-positive, any Ki67); or triple-negative (ER-negative, PR-negative, HER2-negative, any Ki67). Instances with missing subtype data are noted in relevant tables. Thresholds for ER, PR, and Ki67 aligned with standard breast cancer classification (10% and 80% for ER/PR; 15% and 20% for Ki67). A secondary analysis from the two largest contributing COCs examined alternative Ki67 cutoffs (10% and 30%) recommended by the International Ki67 Breast Cancer Working Group.[15]

For genetic evaluation, BRCA1/2 testing employed Sanger sequencing routinely from 2007 onward, with next-generation sequencing (NGS) introduced from 2014, though exact methodologies were not documented in the records.

The investigation focused on characterizing patient profiles, tumor attributes, treatment patterns, genetic testing access, and extended survival outcomes across the entire cohort, with separate assessments for non-metastatic (M0) and de novo metastatic (M1) disease. Cases with M0 status but suboptimal surgical intervention were handled distinctly, particularly in survival evaluations.

Long-term outcomes and statistical methods

Key endpoints comprised recurrence-free interval (RFi), breast cancer-specific mortality (BCSM), and overall survival (OS). RFi represented the duration from surgery to locoregional or distant recurrence among patients with potentially curative M0 disease.[16] OS measured the interval from diagnosis to death irrespective of cause. Individuals without events or lost to follow-up were censored at their last recorded visit. BCSM tracked the period from diagnosis to death attributable to disease progression/relapse, treating other causes of death as competing risks.

Descriptive summaries of patient and treatment variables utilized standard approaches: median with interquartile range (IQR) or mean ± SD for continuous data, and counts with percentages for categorical data. Survival estimates for OS and RFi were derived via Kaplan-Meier curves, with comparisons via log-rank tests. Cumulative incidence functions estimated breast cancer-related death probabilities, tested using Gray's method. Univariable and multivariable modeling employed Cox proportional hazards for OS and RFi, and Fine-Gray subdistribution hazards for BCSM, yielding hazard ratios (HR). Covariates with univariable $P < 0.2$ advanced to multivariable modeling, with final selection via stepwise Akaike information criterion. Follow-up duration was calculated using the reverse Kaplan-Meier approach. Analyses were conducted in R software version 4.2.2[17] at a significance threshold of 0.05.

Results and Discussion

This collaborative retrospective study encompassed 256 individuals identified with MBC across the Czech Republic from 2007 through 2017. Cases were grouped according to extent of disease into non-metastatic (M0; N = 226, 88%) and initially metastatic (de novo M1; N = 30, 12%; **Figure 1**). Within the M0 category, further distinction was made between those treated with curative surgery and systemic therapy (primary M0; N = 201, 89%) and those receiving palliative management due to limited surgical scope (N = 25, 11%).

Patient and tumor features

Diagnosis occurred at a median age of 66 years. A total of 16 patients (6.2%) were under 40 years, whereas 52 (20%) exceeded 75 years.

Advanced stages dominated, with stage II in 37% and stage III in 26%. Central breast involvement was most common (International Classification of Diseases, 10th Revision code C50.1 in 46%). Genetic assessment was carried out in 127 cases (51%), revealing wild-type results in 94 (76%). Deleterious hereditary variants appeared in 30 patients (24%), chiefly BRCA2

alterations (12/103, 12%). Comprehensive overviews of patient and tumor profiles are provided in **Tables 1 and 2.**

Table 1. Patient and tumor characteristics of primary M0 and de novo M1 patients.

Characteristics at diagnosis	De novo M1[2] (*N* = 30)	Primary M0[1] (*N* = 201)
Period of diagnosis		
2007-2010		52 (26%)
2011-2014	5 (17%)	69 (34%)
2015-2017	15 (50%)	80 (40%)
Age at diagnosis (years)	10 (33%)	
Mean (SD)		63 (13)
Median (IQR)		65 (57, 72)
Range	65 (13)	20, 89
≤40	66 (62, 73)	12 (6.0%)
41-50	32, 85	20 (10.0%)
51-60	3 (10%)	38 (19%)
61-65	1 (3.3%)	35 (17%)
66-70	3 (10%)	38 (19%)
71-75	5 (17%)	22 (11%)
>75	9 (30%)	36 (18%)
Genetic testing performed	3 (10%)	106 (54%)
Missing	6 (20%)	4
Results of genetic testing	10 (37%)	
Wild type	3	80 (78%)
BRCA1		5 (4.9%)
BRCA2		12 (12%)
CHEK2	7 (70%)	3 (2.9%)
Other	1 (10%)	3 (2.9%)
Missing	0 (0%)	3
Location[3]	1 (10%)	
C50.0	1 (10%)	7 (3.5%)
C50.1	0	93 (46%)
C50.2		7 (3.5%)
C50.3		5 (2.5%)
C50.4	0 (0%)	58 (29%)
C50.5	13 (43%)	5 (2.5%)
C50.8	0 (0%)	5 (2.5%)
C50.9	0 (0%)	21 (10%)
Stage	11 (37%)	
0 (DCIS)	0 (0%)	4 (2.0%)
I	3 (10%)	57 (29%)
II	3 (10%)	87 (44%)
III		51 (26%)
IV		0 (0%)
Missing	0 (0%)	2
cT	0 (0%)	
Tis	0 (0%)	4 (2.1%)
1	0 (0%)	84 (44%)
2	30 (100%)	74 (38%)
3	0	3 (1.6%)

4		28 (15%)
Missing	0 (0%)	8
cN	3 (11%)	
0	6 (21%)	100 (55%)
1	3 (11%)	68 (38%)
2	16 (57%)	9 (5.0%)
3	2	4 (2.2%)
Unknown		20
Site of relapse or metastasis		
None	4 (15%)	129 (73%)
Locoregional	11 (42%)	13 (7.4%)
Bone	5 (19%)	11 (6.2%)
Visceral	6 (23%)	14 (7.4%)
Combination	4	23 (13%)
Unknown		11
	0 (0%)	
	3 (10%)	
	8 (27%)	
	0 (0%)	
	19 (63%)	
	0	

1Primary M0: patients with non-metastatic disease who underwent surgery and treatment with a curative intent.
2De novo M1: patients with de novo metastatic disease.
3According to International Classification of Diseases, 10th Revision, diagnostic codes.

Abbreviations: IQR, interquartile range; DCIS, ductal carcinoma in situ; cT, clinical T stage; Tis, carcinoma in situ; cN, clinical N stage.

Table 2. Pathological characteristics of primary M0 and de novo M1 patients.

Pathological characteristic	De novo M1[2] (*N* = 30)	Primary M0[1] (*N* = 201)
Histological subtype		
DCIS		4 (2.0%)
IDC (NST)	0 (0%)	177 (88%)
IDC+ILC	25 (83%)	2 (1.0%)
Mucinous	0 (0%)	3 (1.5%)
Invasive papillary	0 (0%)	10 (5.0%)
Other	3 (10%)	5 (2.5%)
Grade	2 (6.7%)	
1		19 (9.8%)
2		96 (50%)
3	3 (10%)	78 (40%)
Missing	16 (53%)	8
Ki67 proliferation index (%)	11 (37%)	
1-14	0	45 (23%)
15-20		31 (16%)
>20		118 (61%)
Missing	5 (19%)	7

ER (%)	3 (11%)	
<10	19 (70%)	5 (2.5%)
10-79	3	26 (13%)
80-100		169 (84%)
Missing		1
PR (%)	3 (10%)	
<10	0 (0%)	27 (14%)
10-79	26 (90%)	69 (35%)
80-100	1	104 (52%)
Missing		1
HER2		
Negative	8 (28%)	171 (87%)
Positive	11 (38%)	25 (13%)
Missing	10 (34%)	5
Clinicopathological subtypes[3]	1	
Luminal A-like, HER2–		35 (18%)
Luminal B-like, HER2–		132 (68%)
Luminal B-like, HER2+	25 (86%)	24 (12%)
HER2+ (non-luminal)	4 (14%)	1 (0.5%)
TNBC	1	3 (1.5%)
Unknown		6[4]
pT		
0/Tis	2 (6.9%)	6 (3.0%)
1	21 (72%)	92 (46%)
2	3 (10%)	84 (42%)
3	1 (3.4%)	3 (1.5%)
4	2 (6.9%)	13 (6.6%)
Unknown	1	3
pN		
0		105 (52%)
ITC	0 (0%)	2 (1.0%)
1mi	3 (43%)	4 (2.0%)
1	3 (43%)	58 (29%)
2	1 (14%)	23 (12%)
3	0 (0%)	8 (4.0%)
Unknown	23	1
	2 (29%)	
	1 (14%)	
	0 (0%)	
	1 (14%)	
	2 (29%)	
	1 (14%)	
	23	

1Primary M0: patients with non-metastatic disease who underwent surgery and treatment with a curative intent.
2De novo M1: patients with de novo metastatic disease.
3Ki67 was unknown in 9 HER2– cases; one G1 case was classified as luminal A-like, 2 G3 cases were classified as luminal B-like, 4 G2 cases with PR of 0-79 were classified as luminal B-like, and 2 cases were unknown.

4Five cases were hormone receptor-positive (4 with unknown HER2 and one HER2−), one had unknown ER, PR, HER2, and Ki67 status.

Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ITC, isolated tumor cells; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, receptor type 2 for human epidermal growth factor; TNBC, triple-negative breast cancer; pT, pathological T stage; Tis, carcinoma in situ; pN, pathological N stage; 1mi, micrometastasis present in lymph node.

For the primary M0 subset (N = 201), early-stage (I) presentation was limited to 29%, even though small tumors (pT0/Tis/T1) comprised 49% and node-negative pathology (pN0) reached 53%. The prevailing histology was invasive carcinoma of no special type (NST; N = 177, 88%), once known as invasive ductal carcinoma. Well-differentiated (G1) lesions made up merely 9.8%, with low Ki67 in 23%. In contrast, poor differentiation (G3) and high Ki67 (>20%) featured in 40% and 61%, respectively. Hormone-responsive, HER2-nonexpressing tumors dominated (N = 171, 87%), including strong ER positivity in 84%, though luminal A-like classification applied to only 18%. Luminal B-like, HER2-negative emerged as the chief molecular profile in 68%. Extended pathological descriptions are available in **Table 2**.

In the de novo M1 group of 30 patients, isolated bone spread affected 8 (27%), purely locoregional extension 3 (10%), and multiple sites 19 (63%). Thorough clinicopathological summaries appear in **Tables 1 and 2.**

Treatment

Primary M0 patients

Management details for the curative primary M0 group (N = 201, 89%) are listed in **Table 3**. Lumpectomy or breast-conserving procedures were uncommon, involving just 7 cases (3.5%), despite 4 pure in situ diagnoses and 84 (44%) with T1 primaries. Standard operation was modified radical mastectomy (ME), documented in 194 patients (97%). Sentinel node sampling occurred in 69 individuals (34%), roughly half (51/105) of whom were clinically node-free.

Table 3. Treatment characteristics of primary M0 patients

Characteristic	Value (N = 201)
Neoadjuvant therapy	27 (13%)
Anthracycline	2 (7.4%)
Anthracycline + taxane	16 (59%)
Taxane	1 (3.7%)
Endocrine therapy (ET)	6 (22%)
Chemotherapy + ET	2 (7.4%)
Anti-HER2 therapy during neoadjuvant treatment	1/6 (17%)
Type of breast surgery	
Breast-conserving surgery (BCS)	7 (3.5%)
Mastectomy (ME)	194 (97%)
Type of nodal surgery	
Sentinel lymph node biopsy (SLNB)	69 (34%)
Axillary lymph node dissection	132 (66%)
Adjuvant chemotherapy	87 (44%)
Unknown	1
Adjuvant chemotherapy regimen	
Anthracycline	51 (59%)
Anthracycline + taxane	32 (37%)
Taxane	3 (3.4%)
Capecitabine	1 (1.1%)
Discontinuation of adjuvant chemotherapy[1]	10 (12%)
Adjuvant endocrine therapy (ET)	180 (90%)
Unknown	1
Type of endocrine therapy	

Tamoxifen	134 (74%)
Aromatase inhibitor (AI)	28 (16%)
Tamoxifen followed by AI	18 (10%)
Duration of endocrine therapy (months)[2]	
Median (IQR)	60 (38–65)
Range	2–119
Missing	11
≥5 years	104 (62%)
<5 years	65 (38%)
Reason for discontinuation of ET[1]	61 (36%)
Disease recurrence or death	50 (85%)
Poor performance status, intolerance, or refusal	9 (15%)
Missing	2
Ovarian suppression/castration therapy	17 (9.2%)
Missing	16
Anti-HER2 therapy in adjuvant setting	22/25 (88%)
Radiotherapy (RT)	96 (48%)
Unknown	1
Radiotherapy target regions	
Breast/chest wall only	7 (7.3%)
Breast/chest wall + regional nodes	88 (92%)
Regional nodes only	1 (1.0%)

1Primary M0: patients with non-metastatic disease who underwent surgery and treatment with a curative intent.
2CT discontinuation was defined as less than the standard number of treatment cycles in adjuvant setting; for ET discontinuation, it has been considered less than 5 years of the adjuvant ET.
334/180 patients continued treatment at the evaluation date.

Abbreviations: ET, endocrine therapy; CT, chemotherapy; HER2, human epidermal growth factor receptor type 2; BCS, breast-conserving surgery; ME, radical mastectomy; SLNB, sentinel lymph node biopsy; AI, aromatase inhibitor; IQR, interquartile range; RT, radiotherapy.

Adjuvant radiotherapy was recommended for 91 (47%) individuals following radical mastectomy. Among 98 cases with pT1/pT2 and pN0 compared to 77 with pN+ status, radiotherapy was prescribed in 22% versus 71%, respectively **(Table 4).** Most (70%) node-positive patients received irradiation to the chest wall and regional lymph nodes. Five out of 7 individuals who had breast-conserving procedures also received radiotherapy; it was not given to 2 cases with pT1/T2 pN0 disease.

Preoperative systemic treatment was prescribed for 27 (13%) cases. The median age in this group was 61 years, with 77% presenting stage III and 23% stage II. Chemotherapy was used in 19 (73%), endocrine treatment in 6 (22%), and a combination of both in 2 (7%).

Postoperative endocrine treatment was documented in 180 (90%) cases. Among 196 hormone receptor-positive individuals, only 15 (7.7%) did not receive it. Tamoxifen, the preferred option, was prescribed to 152 (84%). Of 46 (26%) treated with aromatase inhibitors, just 11 (24%) also received LHRH analogs **(Table 5).** Overall, 17 (9.2%) received LHRH analogs combined with endocrine agents.

Postoperative chemotherapy was given to 87 (44%) cases. Anthracycline-containing protocols dominated in 51 (59%), while sequential anthracyclines followed by taxanes were used in 32 (37%). Among 25 HER2-overexpressing tumors, 22 (88%) received targeted anti-HER2 agents, including 16 combined with chemotherapy and 6 with endocrine therapy or anti-HER2 alone.

Chemotherapy was not completed in 10/87 (12%) cases. Only 9/169 (5%) received less than 5 years of postoperative endocrine treatment unrelated to recurrence or mortality. Discontinuation details are provided in **Table 3.**

De novo M1 patients

In the group of 30 individuals with initial metastatic disease, palliative mastectomy without radiotherapy was carried out in 8 (27%; **Table 6**). Seven of these had non-visceral spread limited to lymph nodes and/or bone. Radiotherapy was delivered to 14 (47%) metastatic cases.

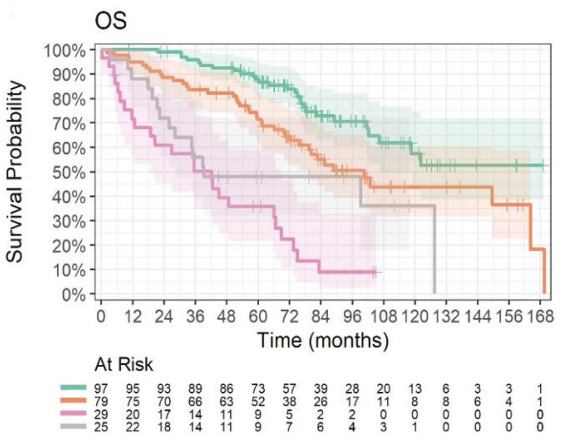
Locoregional irradiation was used in 8 non-operated patients, while palliative irradiation to metastatic sites occurred in 6. First-line systemic palliative therapy was provided to 29 (97%). Among 23 with luminal HER2-negative disease, 13 (57%) received endocrine therapy, 2 (9%) chemotherapy, and 7 (30%) both chemotherapy and subsequent maintenance endocrine therapy. The approach for one remaining case was not recorded.

Palliative-intent M0 patients

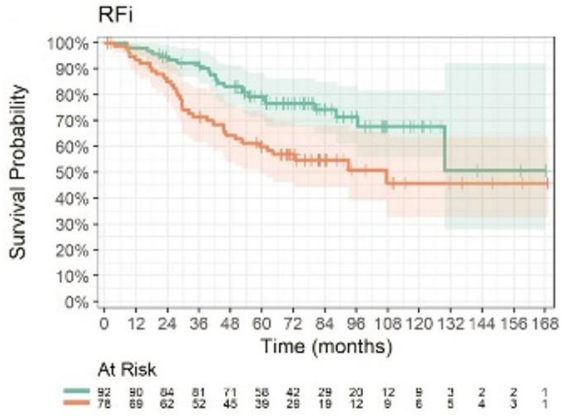
Of 25 non-metastatic cases managed palliatively, 12 (48%) had no surgery, while 13 (52%) had suboptimal resection of the breast and/or axillary nodes (1 breast only, 9 nodes only, and 3 both). Radiotherapy was administered to 12 patients (6 non-operated and 6 post-suboptimal surgery), comprising chest wall plus axilla in 5 (42%), breast alone in 1 (8%), and breast plus axilla in 6 (50%). Overall, 22 (88%) received endocrine therapy and 5 (21%) chemotherapy as initial palliative systemic treatment.

Long-term outcomes

Over a median follow-up of 90 months (95% CI 82-98 months), 116 (45%) individuals deceased. This included 76/201 (38%) curative primary M0 cases, 15/25 (60%) palliative M0 cases, and 25/30 (83%) de novo M1 cases**.** Median overall survival was 122 months for primary M0, 42 months for de novo M1, and 39 months for palliative M0 cases **(Figure 2a; Table 8).** Five-year overall survival rates reached 80%, 36%, and 48% in the respective groups. In primary M0, median overall survival was not reached for node-negative and was 101 months for node-positive cases (**Table 8**).



a)



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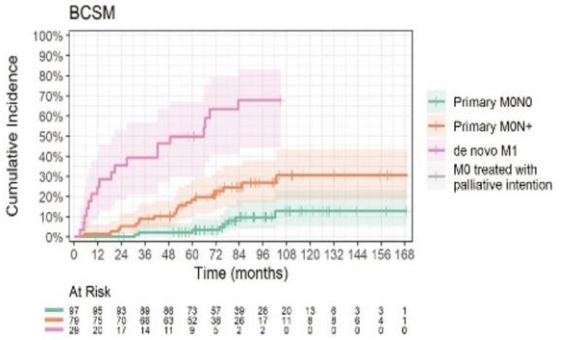


c)

Figure 2. Kaplan-Meier estimates of (a) overall survival and (b) RFi, and cumulative incidence estimates of (c) BCSM according to the stage at diagnosis.

Within primary M0 cases, recurrence affected 61 (32%) during follow-up. Median recurrence-free interval was not reached overall or in node-negative subgroups, but reached 108 months in node-positive **(Figure 2b; Table 8).**

Five-year breast cancer-specific mortality stood at 9.5% for primary M0 and 50% for de novo M1. In M0 cases, it was 2.2% for node-negative and 18% for node-positive **(Figure 2c; Table 8).**

Univariable and multivariable assessments of prognostic factors in primary M0 cases are shown in **Table 4**. Age influenced overall survival ($P < .002$) but not breast cancer-specific endpoints (RFi and BCSM). Stage, T category, and N category impacted all endpoints, especially breast cancer-related ones. Grade affected recurrence-free interval ($P = .004$, **Figure 3a**) and breast cancer-specific mortality ($P = .023$, **Figure 3b**). Among molecular markers, progesterone receptor status and

Ki67 index showed associations. For progesterone receptor, intermediate expression (10%-79%) yielded the poorest results, nearing significance for recurrence-free interval (P = .052, **Figure 3c**) and significant for overall survival (P = .008) and breast cancer-specific mortality (P = .043, **Figure 3d**). Ki67 index correlated with overall survival (P = .034), recurrence-free interval (P < .001; **Figure 3e**), and breast cancer-specific mortality (P = .018; **Figure 3f**). A secondary evaluation using alternative Ki67 cutoffs (10% and 30%) in data from the two major centers (82 cases total; **Figure 1**) confirmed worse outcomes for Ki67 >30%, with hazard ratio 2.27 for recurrence-free interval (P = .048) and 4.08 for breast cancer-specific mortality (P = .022).

Table 4. Univariable and multivariable assessments of clinicopathological factors influencing overall survival, RFi, and BCSM among primary M0 patients managed with curative intent.

Variable	N	OS Univariable HR (95% CI)	P*	OS Multivariable HR (95% CI)	P*	RFi Univariable HR (95% CI)	P*	RFi Multivariable HR (95% CI)	P*	BSCM Univariable HR (95% CI)	P†	BSCM Multivariable HR (95% CI)	P†
Age at diagnosis (years)													
≤40	68	Reference	.002	Reference	.002	Reference	.279	Reference	.321	—	—	—	—
61–70	72	2.01 (1.06, 3.81)	—	1.90 (0.98, 3.68)	—	0.71 (0.40, 1.26)	—	1.10 (0.50, 2.42)	—	—	—	—	—
>70	56	3.02 (1.59, 5.74)	—	3.32 (1.69, 6.53)	—	0.62 (0.32, 1.20)	—	0.50 (0.17, 1.46)	—	—	—	—	—
Stage													
I	54	Reference	.076	Reference	.007	Reference	<.001	Reference	.001	Reference	.002	—	—

0, ITC	**Nodal status (pN)**	3–4	2	1	0, Tis	**Primary tumor (pT)**	III	II
104		16	83	88	6		49	87
Reference		2.61 (1.26, 5.40)	1.27 (0.76, 2.12)	Reference	0.64 (0.09, 4.69)		2.10 (1.09, 4.03)	1.47 (0.80, 2.71)
.070		—	—	—	.055		—	—
Reference		3.11 (1.38, 7.00)	1.64 (0.94, 2.84)	Reference	NS		3.08 (1.51, 6.31)	1.75 (0.89, 3.40)
<.001		—	—	—	.012		—	—
Reference		7.32 (2.49, 21.5)	2.45 (1.02, 5.87)	Reference	NS		4.40 (2.07, 9.35)	1.98 (0.92, 4.24)
<.001		—	—	—	<.001		—	—
Reference		5.76 (1.93, 17.2)	1.90 (0.77, 4.69)	Reference	NS		3.61 (1.56, 8.34)	1.44 (0.61, 3.40)
.074		—	—	—	<.001		—	—
—		—	—	—	—		6.52 (1.95, 21.8)	2.59 (0.74, 9.04)
—		—	—	—	—		—	—
—		—	—	—	—		—	—
—		—	—	—	—		—	—

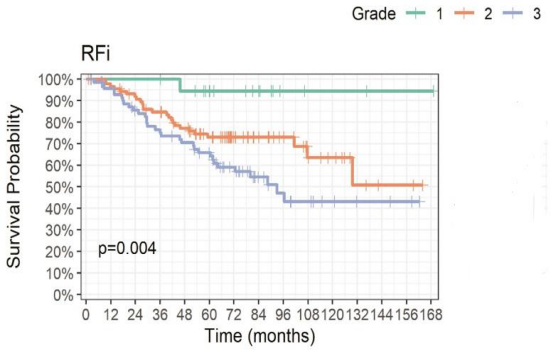
Luminal A–like	HER2+	**Clinicopathological subtype**	3	2	1	**Histological grade**	2–3	1mi, 1
34	24		77	93	19		29	62
1.41 (0.53, 3.77)	Reference		1.19 (0.74, 1.94)	Reference	0.48 (0.17, 1.35)		2.04 (1.07, 3.91)	1.47 (0.88, 2.47)
—	.474		—	—	.198		—	—
0.18 (0.05, 0.67)	Reference		1.70 (1.00, 2.86)	Reference	0.16 (0.02, 1.15)		3.59 (1.91, 6.74)	1.64 (0.91, 2.96)
—	—		—	—	.004		—	—
0.31 (0.06, 1.66)	Reference		1.47 (0.80, 2.71)	Reference	0.26 (0.03, 1.96)		5.95 (2.37, 14.9)	2.63 (1.07, 6.41)
—	—		—	—	.083		—	—
0.70 (0.12, 4.26)	Reference		1.91 (0.93, 3.95)	Reference	NS		3.00 (1.17, 7.69)	1.72 (0.69, 4.26)
—	—		—	—	<.001		—	—
—	—		1.54 (0.68, 3.47)	Reference	NS		—	—
—	—		—	—	<.001		—	—
—	—		—	—			—	—
—	—		—	—			—	—

80–100	10–79	<10	**PR (%)**	80–100	10–79	<10	**ER (%)**	TNBC	Luminal B–like
102	66	27		167	23	5		3	131
1.57 (0.65, 3.76)	2.89 (1.21, 6.91)	Reference		0.79 (0.19, 3.24)	1.08 (0.24, 4.85)	Reference		NS	1.85 (0.79, 4.31)
—	—	.008		—	—	.588		—	—
1.28 (0.52, 3.15)	2.52 (1.02, 6.19)	Reference		0.59 (0.14, 2.43)	0.63 (0.13, 2.98)	Reference		NS	0.96 (0.49, 1.91)
—	—	.021		—	—	.755		—	—
1.75 (0.68, 4.53)	2.77 (1.06, 7.24)	Reference		0.80 (0.10, 6.35)	0.57 (0.06, 5.83)	Reference		NS	1.09 (0.38, 3.13)
—	—	.052		—	—	.832		—	—
3.16 (1.06, 9.41)	3.38 (1.14, 10.0)	Reference		—	—	—		NS	0.98 (0.32, 3.04)
—	—	.038		—	—	—		—	—
0.97 (0.26, 3.58)	2.41 (0.68, 8.52)	Reference		—	—	—		—	—
—	—	.045		—	—	—		—	—
—	—	—		—	—	—		—	—
—	—	—		—	—	—		—	—

HER2 status												
Negative	169	Reference	.198	Reference	.091	Reference	.393	Reference	.814	—	—	—	—
Positive	24	0.58 (0.25, 1.34)	—	0.49 (0.20, 1.20)	—	1.34 (0.68, 2.65)	—	1.13 (0.40, 3.25)	—	—	—	—	—
Ki67 (%)												
1–14	43	Reference	.034	Reference	.008	Reference	<.001	Reference	.114	Reference	.033	—	—
15–20	31	0.67 (0.25, 1.77)	—	0.51 (0.19, 1.37)	—	3.26 (1.00, 10.6)	—	1.42 (0.41, 4.96)	—	2.30 (0.40, 13.4)	—	—	—
>20	115	1.69 (0.91, 3.12)	—	1.59 (0.83, 3.03)	—	5.60 (2.01, 15.6)	—	2.48 (0.83, 7.36)	—	5.35 (1.27, 22.5)	—	—	—

P-values derived from *Cox proportional hazards modeling or †Fine-Gray modeling. Bold formatting indicates statistical significance.

Abbreviations: OS, overall survival; RFi, recurrence-free interval; BCSM, breast cancer-specific mortality; HR, hazard ratio; CI, confidence interval; Ref, reference group; NS, not stated owing to insufficient events; pT, pathological T category; Tis, carcinoma in situ; pN, pathological N category; ITC, isolated tumor cells; 1mi, nodal micrometastasis; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; ER, estrogen receptor; PR, progesterone receptor.



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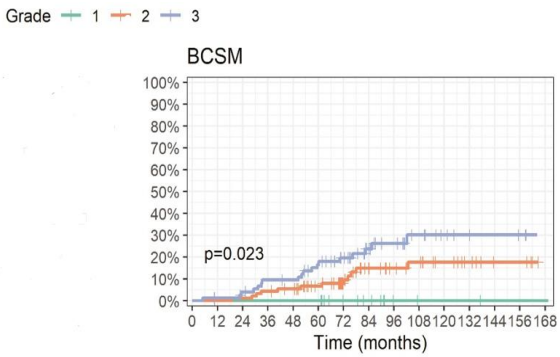

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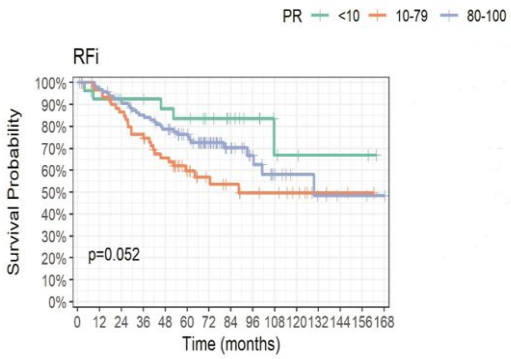

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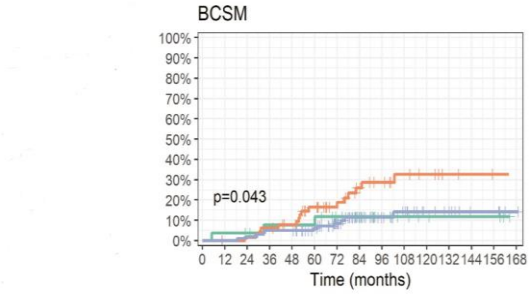

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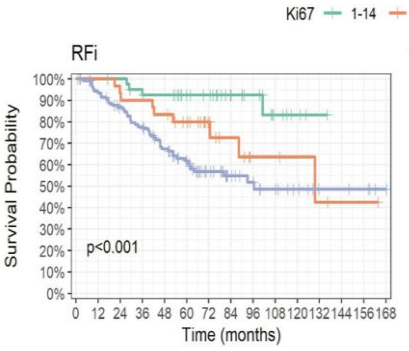

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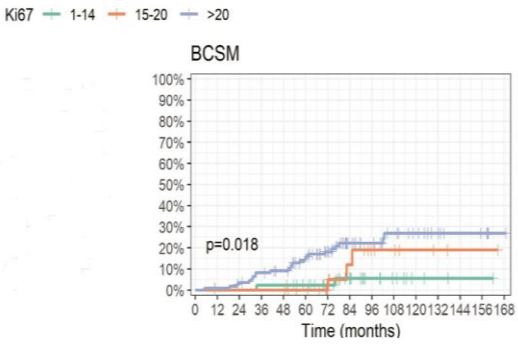
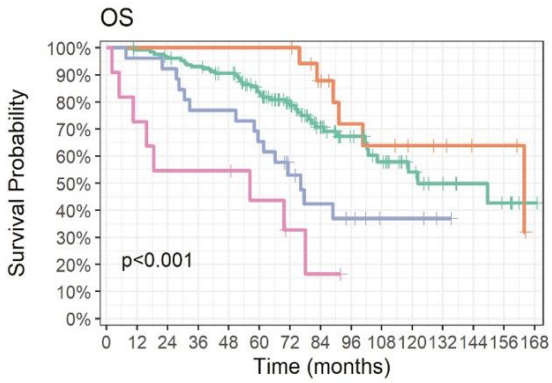


f)

Figure 3. Kaplan-Meier curves for RFi (left panels) and cumulative incidence curves for BCSM (right panels). (a) RFi and (b) BCSM stratified by histological grade. (c) RFi and (d) BCSM by progesterone receptor levels. (e) RFi and (f) BCSM by Ki67 proliferation index. P-values calculated via log-rank test for RFi and Gray's test for BCSM.

Multivariable modeling **(Table 4)** identified age, overall stage, HER2 status, PR expression, and Ki67 as independent factors for OS; stage, grade, PR, and Ki67 for RFi; and clinicopathological subtype, pT, pN, and grade for BCSM.

Treatment impacts on endpoints were examined through univariable models adjusted for key variables (age, T stage, N stage, grade, PR, HER2, Ki67) in a subset of 192 hormone receptor-positive individuals with invasive M0 disease. Endocrine therapy demonstrated a clear association with improved RFi ($P < .001$, **Table 9**). Individuals receiving tamoxifen or tamoxifen followed by aromatase inhibitor experienced fewer recurrences compared to those on aromatase inhibitor monotherapy or no endocrine therapy **(Figure 4)**. No corresponding influence was seen on BCSM.



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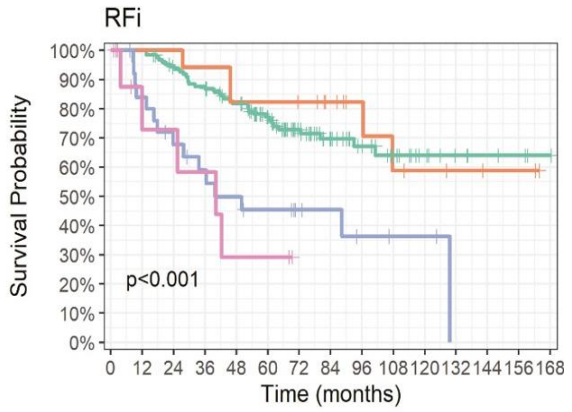

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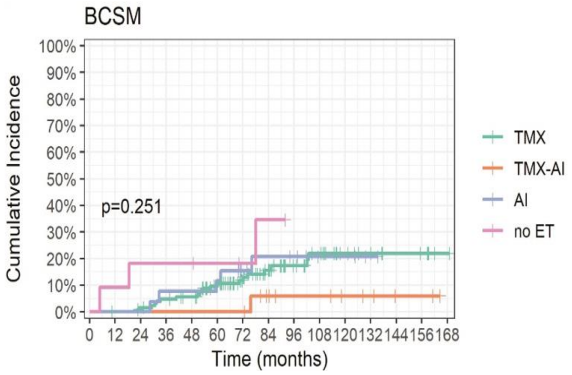

c)

Figure 4. Kaplan-Meier plots of (a) overall survival (OS) and (b) RFi, plus cumulative incidence of (c) BCSM, grouped by endocrine therapy regimen in hormone receptor-positive invasive M0 cases. P-values obtained from log-rank testing for OS and RFi, and Gray's testing for BCSM.

The present work represents the initial nationwide, multicenter retrospective evaluation of MBC within the Czech Republic. Data from 256 cases managed at Complex Oncological Centers between 2007 and 2017 were reviewed. Given the annual incidence of roughly 45-65 new diagnoses during this timeframe, the cohort captured approximately half of all national MBC occurrences. Among the 15 existing centers, 9 possessed adequate resources and prior patient consent to contribute data.

Typical MBC diagnosis occurs near age 65; prior reports noted means of 63 years [5] and 65 years [1], or medians of 68 years [6, 7]. In one series, only 1.6% were under 40 years, while 29.3% exceeded 75 years [6]. Our cohort showed a median of 66 years, with 6.2% below 40 years and 20% above 75 years. The highest median age (73 years) appeared in palliatively managed M0 cases, where 14 (56%) had locally advanced stage III disease; 12 of 25 avoided surgery, including 6 who received locoregional radiotherapy. Advanced age and comorbidities likely contributed to delayed presentation and conservative approaches. The elevated proportion of younger cases remains unexplained but may reflect selection bias toward centralized specialist care preferred by younger individuals, while elderly patients more often receive treatment locally. Age showed no independent association with breast cancer-specific endpoints (RFi, BCSM) in curative M0 cases.

International guidelines recommend genetic counseling and testing for all MBC patients, though access differs widely. Here, 51% underwent evaluation, revealing BRCA2 germline variants in 12% of tested individuals—the predominant alteration [7, 10]. Untested cases may harbor undetected mutations, precluding prognostic analysis of genetic findings. Testing rates varied markedly across centers (3.2% to 85%), though patient acceptance data were unavailable.

Sentinel lymph node biopsy utilization has risen progressively [6, 18]. Approximately one-third of our cases employed this technique, consistent with contemporary Chinese findings [17].

Published series indicate over 80% NST histology (formerly invasive ductal) [5-8], nodal involvement around 30% for N1 and 5%-9% for N2/3 [1, 5, 6], and metastatic presentation in 5%-9% [5-7]. Luminal B-like, HER2-negative predominates over luminal A-like [19], though full molecular classification is infrequent beyond immunohistochemistry. Aggressive traits like elevated Ki67 or grade 3 affect 25%-33% [5, 6]. Compared to literature, our population exhibited several unfavorable attributes: a higher de novo metastatic rate (12%), and among curative M0 cases, a greater frequencies of stage III (26%), pN2/3 (16%), grade 3 (40%), high Ki67 (61%), and luminal B-like profile (68%).

The elevated rate of initially metastatic cases in our cohort aligns with findings from Brazil (11.48%) [20] and a predominantly European population (12%) [21]. Semedo [22] reported 8.9% stage IV diagnoses in the SEER database for 2011-2016. Although more aggressive biology might be expected in younger metastatic patients, median ages were comparable between de novo M1 and primary M0 groups (66 vs 65 years). Late detection in this non-screened group likely contributes to the increased stage IV frequency. Surgical intervention in metastatic cases may reflect limited metastatic burden (bone-only or nodal/bone in 7 of 8

operated patients) and/or preoperative clinical assessment.

T and N category distributions across the entire cohort resembled those described by Yao [5], though stage III was more frequent here (26% vs 14%) than in Wang [4]. Primary M0 cases also showed higher pN2/3 involvement than Cardoso's series (16% vs 7.8%) [6]. Regarding additional features in M0 disease, prior reports noted grade 3 in 30%-35% [1, 5, 6], versus 40% in our population. Ki67 assessment, uncommon elsewhere but routine in Czech practice, used the 2013 St Gallen threshold of >20% for high proliferation [23]. Low Ki67 (<15%) paralleled Cardoso's definition. That study found low values (1%-14%) in 61% and high (>20%) in 25% [6], while we observed low in 23% and high in 61%. With low PR (<10%) in only 14%, the predominance of luminal B-like subtype (68%) largely stemmed from elevated Ki67. We verified Ki67's prognostic role for RFi and BCSM, with poorer outcomes at higher levels—further accentuated using a >30% cutoff in subset analysis. This marker may thus guide adjuvant chemotherapy decisions, particularly in node-negative cases, as elaborated later.

Of 196 hormone receptor-positive M0 individuals, 31% with node-negative disease (N = 103) received chemotherapy, while 92% received adjuvant endocrine therapy. Overall, neo-/adjuvant chemotherapy was administered to 106/201 (53%), mirroring the prevalence of luminal B-like biology. Cardoso indicated chemotherapy in only 29.8% despite 48.6% luminal B-like, 24.7% high Ki67 (>20%), and 27% grade 3 [6]. Their longer study period likely captured evolving trends toward greater chemotherapy use.

Adjuvant endocrine therapy was prescribed to 92% of hormone receptor-positive M0 cases—a markedly higher rate than earlier reports of 57.9% [4, 24], 67.3% [25], and 76.8% [6]. Discontinuation unrelated to progression or death occurred in just 5%, due to performance status, intolerance, or refusal. Regional practices, institutional structure, and care standards likely influence these differences.

Individuals receiving tamoxifen (N = 133) exhibited better outcomes than those on aromatase inhibitor monotherapy (N = 28), consistent with known pharmacological limitations of aromatase inhibitors in males [26, 27]. Among 18 switched from tamoxifen to aromatase inhibitor, 7 (39%) received concomitant castration. In contrast, only 4 (14%) on upfront aromatase inhibitor had castration. Prior tamoxifen exposure or lack of gonadotropin suppression in aromatase inhibitor-only cases may underlie the observed RFi and OS disparities. Though few, such suboptimal regimens warrant scrutiny. No other therapeutic deviations from international patterns emerged.

Survival in our series primarily reflected disease extent, in line with global evidence. Cardoso noted median OS of 10.4 years (N0M0), 8.4 years (N+M0), and 2.6 years (M1) [6]. Our 5-year OS reached 80% for M0 and 36% for M1. Comparable figures include 82.8% 5-year OS in over 2000 primary cases (2005-2010) per Liu [28], and 77.6% overall or 21.4% for stage IV in 16 000 diagnoses (2004-2014) [4].

Among prognostic markers, reduced PR expression was associated with inferior OS (P = .008) and BCSM (P = .045), nearing significance for RFi (P = .052). Inter-assay variability could affect PR measurement reliability. Previous works found no OS impact from PR [29, 30]. While Cardoso reported influences of ER, PR, and androgen receptor [6], their receptors underwent central re-evaluation within a prospective trial, unlike our decentralized pathology from nine institutions.

Study strengths include comprehensive documentation of stage details, T/N categories, tumor site, genetic testing access, and Ki67 elements seldom emphasized previously. Limitations arise chiefly from retrospective design and multi-institutional variability without central pathology review. As tertiary referral centers, Complex Oncological Centers may over-represent younger, advanced, or complex cases needing specialized options, introducing selection bias—though also enabling broader treatment availability. The analysis lacked power for direct outcome comparisons with individual reports; thus, prognostic inferences rely on indirect benchmarking.

Conclusion

This nationwide retrospective review encompassed 256 MBC cases diagnosed and managed in Czech centers from 2007 to 2017. Chemotherapy was frequently prescribed in M0 disease, commensurate with luminal B-like prevalence and risk profiles. Near-universal endocrine therapy in hormone receptor-positive patients highlights robust care delivery. Aromatase inhibitor monotherapy without suppression adversely influenced prognosis in hormone-sensitive disease. Indirect benchmarking indicates outcomes comparable to published international series.

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Conflict of Interest: None

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Ethics Statement: This non-interventional retrospective study was approved by the Institutional Ethical Committee of MMCI (protocol code 2023/825/MOU). Before starting treatment, all patients signed written informed consent to process personal information for scientific purposes as part of the documents concerning patient rights.

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