Received: 24 August 2022 | Revised: 12 October 2022 | Accepted: 17 October 2022

DOI: 10.1111/ajco.13893

ORIGINAL ARTICLE

WILEY

Oncological outcomes for encapsulated papillary carcinoma of the breast: Multicentric study of Turkish Society for Radiation Oncology breast cancer study group (TROD 06–014 study)

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Funding information
The authors received no specific funding for this work.

Abstract

Background: Encapsulated papillary carcinoma (EPC) is a rare malignant papillary breast cancer accounting for approximately .5%–2% of all breast tumors. The aim of this multicenter study was to evaluate clinicopathologic features of EPC in addition to oncological outcomes and radiotherapy (RT) details.

Methods: From 10 different academic hospitals in Turkey, we obtained pathology reports of 80 patients with histologically confirmed EPC between 2005 and 2022. Demographic, diagnostic, and treatment data were collected from medical records, retrospectively. Local failure, distant progression, toxicity-adverse effects, overall survival (OS), and disease-free survival were evaluated, and survival analyzes were performed using the Kaplan–Meier method.

Results: Eighty patients with the diagnosis of misspelled sorry (ECP) were retrospectively evaluated. The median age of the patients was 63 (range, 35–85). After a median follow-up of 48 (range; 6–206) months, local recurrence was observed in three patients

(4%). Local recurrence was less common in the patients who received whole breast RT with a tumour bed boost ($p = .025$). There were not any distant metastasis or disease-related death. RT was applied to 61% of the cases, and no treatment-related grade 3 or higher toxicity was reported in any of the patients. Five year OS, cancer-specific survival (CSS), and were observed as 85%, 100%, and 96%, respectively.

Conclusions: ECP is a rare, slow-progressing breast carcinoma associated with good prognosis, it is a disease of elderly patient, and usually occurs in post-menopausal women. It responds extremely well to optimal local treatments and appropriate adjuvant treatments on a patient basis, and has excellent OS and CSS ratios.

KEYWORDS
breast cancer, encapsulated papillary carcinoma, intracystic papillary carcinoma, papillary neoplasms, radiotherapy

1 | INTRODUCTION

Papillary neoplasms of the breast have a wide spectrum ranging from benign formations to malignant structures including intraductal papilloma, papillary ductal carcinoma in situ, solid papillary carcinomas, and encapsulated papillary carcinomas (EPCs). "Encapsulated papillary carcinoma (EPC)," commonly known as intracystic papillary carcinoma, is a rare histological subtype of breast cancer and constitutes approximately .5%-2% of all breast carcinomas.[1,2]

According to the invasive component of the disease, current World Health Organization (WHO) classification, which was published in 2019, categorized ECPs as "EPC-in situ" and "EPC with invasion".[3,4] In addition, other histological types such as ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC) may accompany this pure encapsulated formation.

It is well known that local recurrence and distant metastasis are much more favorable in ECP when compared to IDCs. Close surgical margin and the presence of invasive component are the leading risk factors for disease recurrence. The current literature evidence suggested that the rate of axillary involvement is as low as 3% for EPCs.[5] Although it is rare, axillary metastasis can be encountered; therefore, sentinel lymph node sampling is recommended as a part of surgical approach Surgery alone leads excellent survival and local control rates for the patients with ECP. Nevertheless, in the presence of an invasive component, the course of the disease may vary according to the degree of invasion and, extension. Most of the reports in the literature are in the form of case reports, and there are limited data regarding the role of radiotherapy (RT) in the adjuvant setting. ECP still continues to be investigated with respect to tumor biology, immunohistochemical tendency, and its invasive potential. Unfortunately, there are no evidence-based guidelines for the treatment management of this orphan disease. As a rare pathology, our aim is to examine the disease in terms of clinicopathological features, treatment approaches, and responses to treatment.

2 | MATERIALS AND METHODS

2.1 | Patient selection

This national, multicenter, retrospective study was carried out with the participation of 10 academic centers from Turkey. The centers participating in the study were: Prof Dr Cemil Tascioglu City Hospital, Istanbul (23 pts), Istanbul University, Istanbul Faculty of Medicine (15 pts), Hacettepe University Faculty of Medicine, Ankara (10 pts), Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul (10 pts), Tepecik Education and Research Hospital, Department of Radiation Oncology, Izmir (9 pts), Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul (4 pts), Marmara University, Pendik Education and Research Hospital, Istanbul (3 pts), Istanbul Education and Research Hospital, Istanbul (2 pts), Selcuk University, Faculty of Medicine, Konya (2 pts), Necmettin Erbakan University, Faculty of Medicine, Konya (2 pts). Patients with histologically confirmed ECP were evaluated for age, gender, time of diagnosis, tumor immunophenotype and characteristics, disease stage, RT dose, duration, fraction, chemotherapy (CT) regimen, local failure, distant progression, toxicity-adverse effects, OS, and

The patients included into the study if they had (1) histopathologically confirmed EPC, (2) pure EPC and cases with DCIS/IDC disease component, (3) at least 6 months of follow-up period after treatment regardless of RT. Exclusion criteria's were (1) inoperable disease, (2) previous history of RT or systemic agents for other thoracic malignancies, (3) history of chronic active hematological or immunological disease, and (4) male gender.

The study protocol was approved by the Ethics Committee of Istanbul Prof. Dr. Cemil Taşcıoğlu City Hospital (approval number: E-48670771-514.99). The tumors were staged according to the American Joint Committee on Cancer tumor, lymph nodes and distant metastases (TNM) staging system (8th ed., 2017).

2.2 | Treatment characteristics

All the patients underwent surgery. Adjuvant RT, CT, and hormonotherapy were applied in accordance with the multidisciplinary approach, depending on the clinical practice of each academic center.

2.3 | Follow-up and outcomes assessment

After completion of treatment, all patients were followed by treating physician, a medical oncologist, and a general surgeon. Although the follow-up protocol depends on the daily practice of each center; patient follow-ups were generally done every 4–6 months for the first 2 years, then every 6–8 months, and then annually after 5 years. For following up annual mammography, sonographic evaluation (if necessary) and further imaging (in the presence of suspected recurrent/metastatic disease) were performed. Annual gynecological evaluation was performed in patients using tamoxifen, and annual bone mineral density determination was performed in patients using aromatase inhibitors.

2.4 | Statistical methods

The data for continuous variables were expressed as the median (range), and categorical variables were reported as number and percentage. Data distribution was assessed by the Kolmogorov–Smirnov test. In consideration of the sample size, the non-normal distribution of variables was assumed, and nonparametric tests were used for between group comparisons. Therefore, between the EPC-in situ and EPC-with invasion groups, comparisons were made with the Mann–Whitney *U* test for quantitative data and the chi-square test for qualitative data. Endpoint definitions: local failure (time to any locoregional event related to EPC), distant progression (time to any non-regional event related to EPC), OS (time to any death), cancer-specific survival (time to death from EPC), and disease-free survival (time to any event related to EPC). Kaplan–Meier curves were generated for overall survival (OS), disease-free survival (DFS), and significance was assessed using the log-rank test. Statistical analyses were performed using SPSS 25 software (SPSS Inc., Chicago, IL, USA). A probability value of $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics and pathological findings

Table 1 shows the patients characteristics. The median age of the patients was 63 (range, 35–85), and 70% of the cases were postmenopausal. Median follow-up was 48 (range, 6–206) months. Surgical approach and pathological findings were shown in Table 2. All patients underwent surgical intervention. EPC-in situ (EPC-in situ) and EPC with invasion (EPC-inv) account for 60% and 40% of the cases, respectively. DCIS or IDC accompanies 62% of the cases. The median CA 15.3 value at the time of diagnosis was 14.3 (range, 5–46). The median tumor size is 2.1 cm (range: .3–7). Lymph node positivity was present in only five (6%) of the patients, and extracapsular spread (ECE) was observed in 3 of these patients. Lymphovascular space invasion is present in four (5%) of the patients.

TABLE 1 Patient and tumor characteristics

	Patients (*n*: 80,%)
Age	9 (%11)
<50 years	71 (%89)
≥50 years	
Menopausal status	9 (%11)
Premenopause	1 (%1)
Perimenopause	70 (%88)
Postmenopause	
Parity	2 (%2,5)
Nullipara	6 (%7,5)
Primipara	66 (%82)
Multipara	6 (%8)
Grandmultipara	
Smoking	17 (%21)
Former/Current smoker	63 (%79)
Nonsmoker	
Family history	7 (%9)
Yes	73 (%91)
No	
Tumor laterality	41 (%51)
Left breast	39 (%49)
Right breast	
Tumor focality	70 (%87)
Unifocal	7 (%9)
Multifocal	3 (%4)
Multicentric	
Quadrant	30 (%37)
Upper outer	11 (%14)
Lower outer	16 (%20)
Upper inner	6 (%8)
Lower inner	17 (%21)
Central	

3.2 | Adjuvant systemic/endocrine therapy

Estrogen receptor (ER) positivity was found in 94% of the patients; CerbB2 positivity was observed in 6% (five patients). Hormonotherapy was applied to 92% of the patients. Adjuvant CT was administered to 13 patients (16%). Only two patients (2.5%) were treated with Trastuzumab. The applied CT regimens were doxorubicin/cyclophosphamide (AC), AC followed by weekly paclitaxel, epirubicin/cyclophosphamide (EC) followed by weekly paclitaxel, EC and fluorouracil/ epirubicin/cyclophosphamide (FEC) with frequency order (Table 3).

TABLE 2 Surgery and pathological findings

	Patients (*n*: 80)
Type of breast surgery	11 (%14)
Wide local excision	46 (%57)
Breast conserving surgery	15 (%19)
Simple mastectomy	8 (%10)
Modified radical Mastectomy	
Axillary intervention	50 (%63)
Sentinel lymph node biopsy	14 (%17)
Axillary dissection	16 (%20)
No intervention	
EPC group	48 (%60)
EPC in situ	32 (%40)
EPC invasive	
EPC component	25 (%31)
EPC with DCIS	25 (%31)
EPC with IDC	30 (%38)
Pure EPC	
Tumor size	33 (%41)
<2 cm	39 (%49)
2–5 cm	8 (%10)
>5 cm	
Tumor grade	24 (%30)
I	50 (%63)
II	6 (%7)
III	
Estrogen-receptor status	75 (%94)
Positive	5 (%6)
Negative	
Ki 67 status	32 (%52)30 (%48)
<%14	
≥%14	
T stage	47 (%58)
Tis	15 (%19)
T1	13 (%17)
T2	5 (%6)
T3	
N stage	75 (%94)
N0	4 (%5)
N1	1 (%1)
N2	

Abbreviations: EPC, encapsulated papillary carcinoma; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma.

3.3 | RT

RT was applied to 61% (49 patients) of the cases with daily fractions (fr). The most frequently applied RT technique was observed as forward-planned intensity modulated RT (forward-IMRT) (47%). The median RT dose was 50 Gy (range, 40–50 Gy). The prescribed doses were 50 Gy/25fr (36 pts), 48 Gy/24fr (1 pt), 46 Gy/23fr (3 pts), 42.5 Gy/16fr (3 pts), and 40 Gy/15fr (6 pts). For the lumpectomy cavity, a boost dose was applied to 69% of the cases who underwent RT (34 pts). The median boost dose was 10 Gy (range, 10–20 Gy).

TABLE 3 Adjuvant treatment details

	Patients (*n*: 80)
Chemotherapy	67 (%84)
No	13 (%16)
Yes	
Endocrine therapy	27 (%34)
TAM	46 (%58)
AI	31 (%39)
Anastrozol	15 (%19)
Letrozol	7 (%8)
None	
Radiotherapy	49 (%61)
Yes	31 (%39)
No	
RT planning modality	2 (%4)
2-D	23 (%47)
Forward-IMRT	20 (%41)
Inverse-IMRT	4 (%8)
VMAT	
Radiotherapy boost	34 (%69)15 (%31)
Yes	
No	
Axillary RT	75 (%94)
No	1 (%1)
Yes	3 (%4)
SCN+LEVEL III	1 (%1)
SCN +LEVEL I-II-III	
SCN +LEVEL I-II-III+IMC	

Abbreviations: AI, aromatase inhibitor; IMC, internal mammary chain; IMRT, intensity modulated radiotherapy; RT, Radiotherapy; SCN, supra clavicular nodes; TAM, Tamoxifen; VMAT, volumetric arc therapy.

The prescribed boost doses were 20 Gy/10fr (1 pt), 16 Gy/8fr (3 pts), 14 Gy/7fr (4 pts), 12 Gy/6fr (1 pt), and 10 Gy/5fr (25 pts) (Figure 1). Axillary RT was applied to only 6% of all cases (Table 3). There was no radiation-related grade 3 or higher acute/chronic toxicity. The most common reported radiation-related acute toxicities were esophagitis and dermatitis (Table 4).

3.4 | Oncological results

After a median follow-up of 48 months, local recurrence was observed in three patients. Seven patients died due to nondisease reasons. Distant metastasis was not encountered in any of the patients. Among the patients who received RT, it was observed that local recurrence was less common in the patients who received RT boost compared to the patients who did not ($p = .025$, Figure 2). Two of the patients who developed recurrence had a local relapse in the 2nd and 6th years after the initial diagnosis, and mastectomy was performed as a salvage treatment. For the third patient who developed local recurrence, salvage surgery could not be performed due to her age and comorbidities. Therefore, the third patient underwent endocrine therapy for salvage purposes. Five year OS, cancer-specific survival (CSS), and disease-free

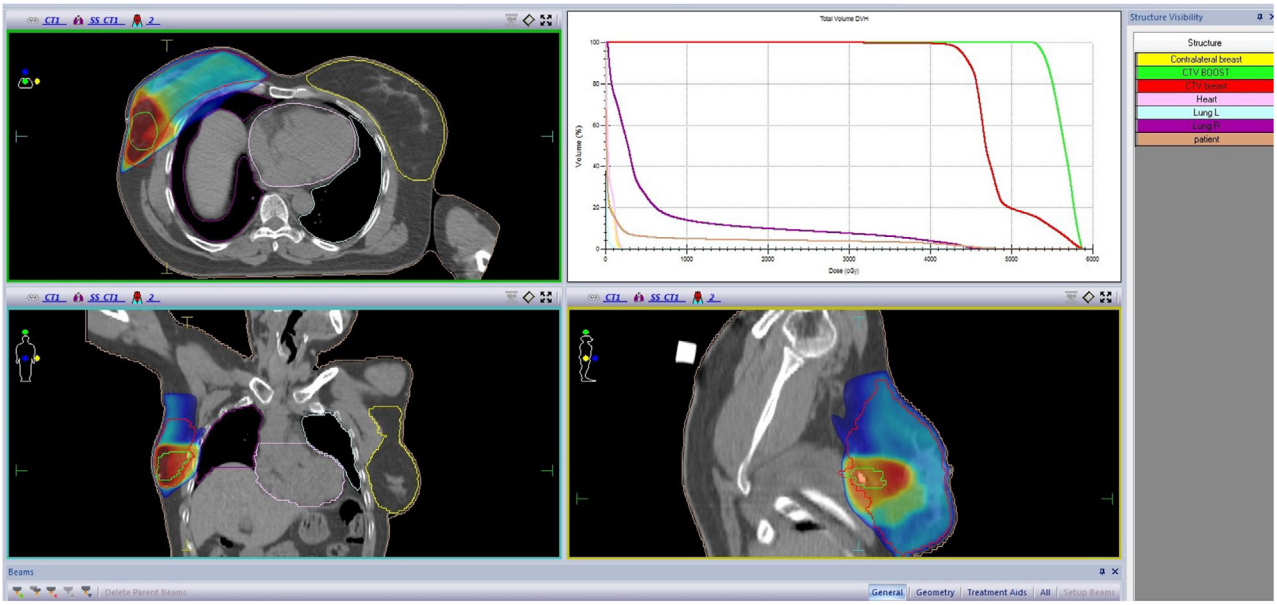

FIGURE 1 An example of the whole-breast and boost radiotherapy (RT) planning. The isodose distribution of axial, sagittal, coronal view for a patient, and the sum dose-volume histogram (DVH). Prescription doses were 42.5 Gy in 16 fractions for the whole-breast and additional 10 Gy in five fractions for the lumpectomy cavity boost, which includes surgical clips in the tumor bed. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Radiation-related toxicities

RT-related acute toxicity	Patients (*n*: 80)
Gr I toxicity	18 (%23)
Dermatitis	2 (%3)
Esophagitis	4 (%5)
Gr II toxicity	0
Dermatitis	
Gr III-V toxicity	
RT-related chronic toxicity	**Patients (*n*: 80)**
Gr I toxicity	9 (%11)
Fibrosis	0
Gr II-V Toxicity	

Abbreviations: Gr, grad; RT, radiotherapy.

survival (DFS) were observed as 85%, 100%, and 96%, respectively (Figure 3A,B).

4 | DISCUSSION

In this multicenter retrospective study of Turkish Society for Radiation Oncology breast cancer study group, we found that most of the patients with the diagnosis of EPC were ≥50 years old, and the histopathological characteristics of the disease were ER positive, low-intermediate grade, and Tis-T1 stage. We did not encounter any prognostic variability between EPC-in situ and EPC-invasive groups. Additionally no prognostic variability was observed according to the inclusion of either IDC or DCIS components. Overall the oncologic outcome was excellent with mild toxicity.

Table 5 shows the selected studies on the EPC of the breast with respect to the treatment outcome and toxicity.[2,5–9] The largest series in the literature investigating the EPC was reported by Mogal et al. in a surveillance epidemiology and results (SEER) database analysis for the period 2000–2009 with 2649 patients.[2] At a median follow-up of 4.8 years; they observed a 4- and 8-year survival rate of 89% and 76%, respectively. Grabowski et al., reported the relative survival rate of 5 and 10 years for EPC (both in situ and invasive) as 97.3% and 95.6%, respectively.[5] In this study, the incidence of distant disease was .4%. Zhang et al. founded 10-year OS, DFS, and CSS rates were reported as 86.5%, 92%, and 100%, respectively.[7] The excellent disease free and OS rates were reported in most of the studies.[2,5–9] Similar to literature data in the current study, we found 5-year OS, CSS, and DFS as 85%, 100%, and 96%, respectively. It supports to favorable clinical prognosis of these tumors.

Importantly, the study by Mogal et al. demonstrated a benefit of adjuvant RT since the lower risk of death was obtained in patients who underwent RT.[2] The authors emphasized that RT can be recommended in patients who underwent Breast Conserving Surgery (BCS). In this study, due to the retrospective nature of the SEER database analysis, it was not possible to obtain information on how many of the patients had invasion or DCIS component. In our study, 61% of the patients received adjuvant RT, and 69% of these patients had invasive disease or DCIS component. Although the effect of whole breast RT alone on local control could not be demonstrated, it was observed that adding boost to whole breast RT reduced local recurrence.

Rakha et al. analyzed the papillary neoplasm data from different centers between 1990 and 2010.[6] According to the current classification, 208 cases of intracystic papillary carcinoma were evaluated, and the median age was 69, the presence of DCIS component was 70%,

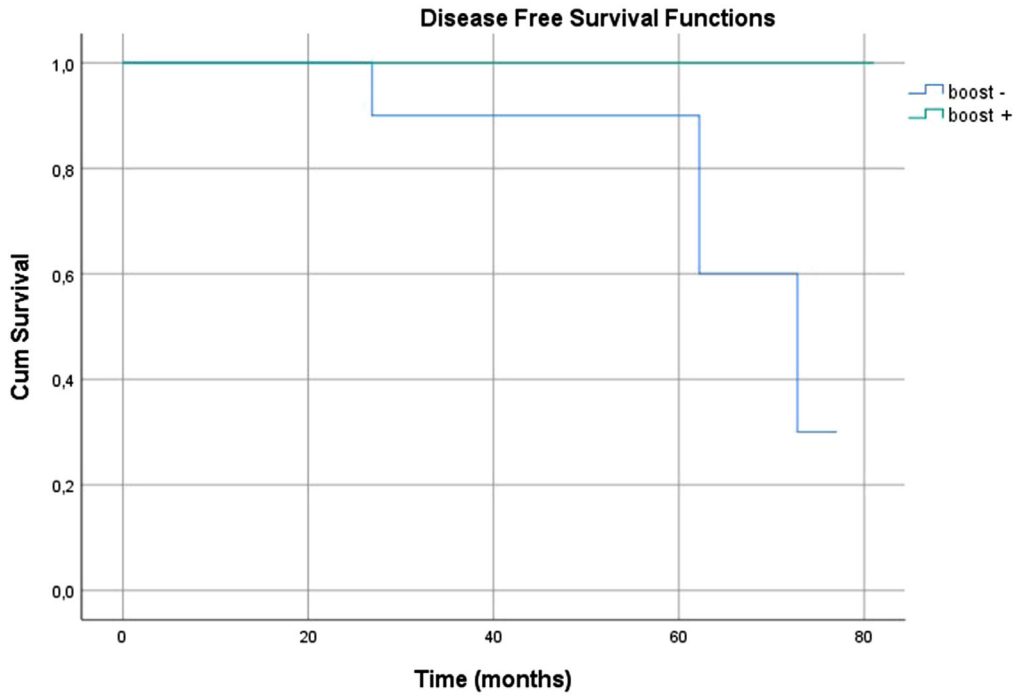

FIGURE 2 Disease free survival curve for boost groups [Colour figure can be viewed at wileyonlinelibrary.com]

lymphatic involvement was 3%, and recurrence in the follow-up period was reported as 8%. In our study, the incidence of both DCIS and IDC components was 31%, and this rate was lower when compared with these two large series in the literature.

Zhang et al. investigated 111 EPC cases diagnosed during the 2004–2017 period and reported that EPC constituted .38% of all breast cancer cases diagnosed in this period.[7] They reported that 62% of the cases were luminal A type, 27% luminal B type, and 10.8% triple negative type, and HER2-overexpression was not observed in any patient. It has been reported that modified mastectomy was applied to 72% of the patients, while BCS was applied to 18%, and the rate of lymphatic involvement was observed as 1.1%. As adjuvant therapy, 23% of the patients received CT, and 8% received RT. At the end of the median 52-month follow-up period, the local recurrence was observed in 2.8% of the patients. In the current study, BCS was applied in 57% of patients, and 61 % and 16% of the patients received adjuvant RT and CT, respectively.

Li et al. also examined 49 cases and reported that HER 2 positivity was 12%, and the rate of lymphatic involvement was 7.7%.[8] In our study, HER 2 positivity was observed at a rate of 6% (five patients), two of these patients were pure EPC cases; the other three cases have an IDC or a DCIS component. In addition, in our study, axillary involvement was observed with a rate of 6% (five patients). Four of these patients were in the EPC invasive group, and all of them have IDC or DCIS components. Jackson et al. reported that they did not see any axillary lymphatic involvement in their series consisting of 25 cases, and they stated that sentinel lymph node biopsy (SLNB) may not be routinely recommended.[9] However, in our study, the cases without any axillary intervention were only 20%, and axillary staging was performed with SLNB in 63% of the patients.

According to the characteristics of most series available in the literature, it is observed that the cases are advanced age, hormone positive, HER 2 (-) and have a low Ki67 index. Moreover, the axillary involvement rate of the patients is generally below 10%, and there is no prognostic difference between the EPC-in situ/EPC-inv groups.[10–15] The median tumor size in the literature is reported as .3–9 cm, while it is 2.1 cm in ours. Also, the incidence of invasive component in the literature varies between 13% and 57%, and the rate of axillary lymphatic involvement is 3%–11%, and these values were 31% and 6%, respectively, in our study. In addition, the rate of local recurrence observed in the literature was reported to be 3.4%–17.2%, and most of these patients were patients with lumpectomy, similar to our study.[16–20]

Our study has limitations that deserve mention. Firstly, the current study has retrospective design; however it is a multicenter study with relatively high sample size. Surgical axillary nodal staging, CT indication, and applied CT regimens differed between centers. Toxicity assessment has also limitations since it was evaluated from retrospective patient records. Most of the EPC-related reports in the literature are in the form of case reports, and the number of cases is limited in the available studies. Therefore, the current study can be considered as one of the most comprehensive studies in the literature in terms of adjuvant treatment results and especially technical features in RT application, prescribed dose and side effect reporting.

Currentdata in the field of encapsulated papillary cancer are limited, so molecular and biological trends, characteristic and prognostic data in mammographic, sonographic and MR imaging, evidence-based axillary approach, adjuvant systemic treatment applications, adjuvant

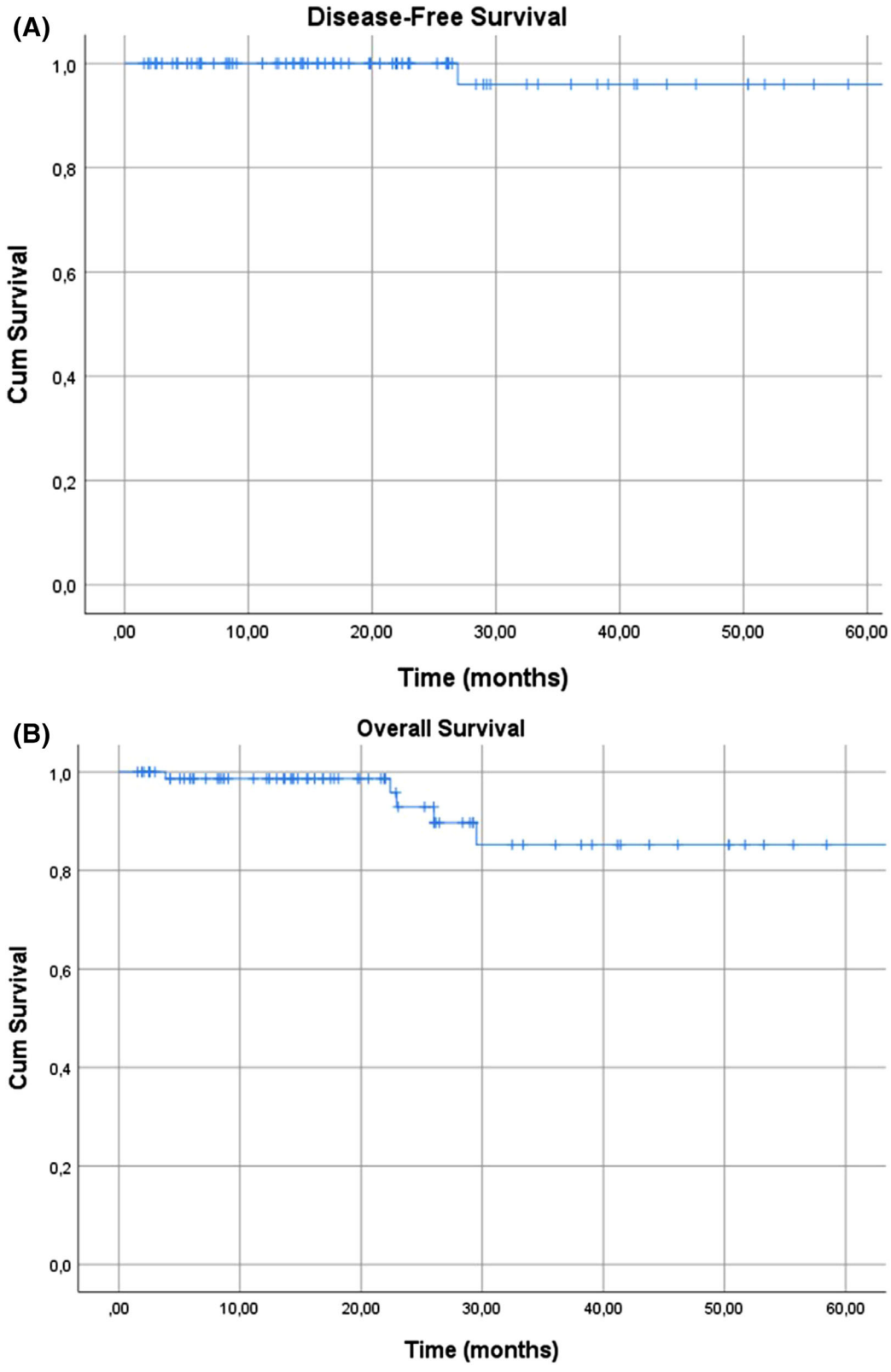

FIGURE 3 Kaplan–Meier plots of (A) disease free survival and (B) overall survival [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Selected studies on the encapsulated papillary carcinoma of the breast: Treatment outcome and toxicity

Study	Total no pts	Management	Local recurrences	Outcomes	Toxicity	Comment
Mogal et al. (2)	2649	Lumpectomy (68.2%) Mastectomy (31.8%) Radiation therapy (34%)	NA	4-year overall survival (89%) 8-year overall survival (76.3%)	NA	SEER database analysis (2000–2009)
Grabowski et al.(5)	917	NA	NA	5-year overall survival (82%) 10-year overall survival (61.2%)	NA	The California Cancer Registry (1988–2005)
Rakha et al. (6)	208	NA	8%	NA	NA	The pathology database at the Nottingham University Hospital national health service Trust (1990–2010)
Zhang et al. (7)	111	Mastectomy (77.5%) Breast-conserving surgery (22.5%) Adjuvant chemotherapy (23.4%) Adjuvant radiation therapy (7.2%) Adjuvant hormonal therapy (84.7%)	2.8%	10-year overall survival (86.5%) 10-year cancer-specific survival (100%) 10-year disease-free survival (92%)	NA	The registry of Tianjin Medical University Cancer Institute and Hospital (2004–2017)
Li X et al. (8)	49	Mastectomy (49%) Breast-conserving surgery (51%) Adjuvant chemotherapy (10.4%) Adjuvant radiation therapy (24.1%) Adjuvant hormonal therapy (65.5%)	10.2%	47-month overall survival (93.10%)	NA	The Tai'an Central Hospital and Qilu Hospital of Shandong University (2004–2014)
Jackson et al. (9)	25	Mastectomy (24%) Breast-conserving surgery (76%) Adjuvant chemotherapy (0%) Adjuvant radiation therapy (53%) Adjuvant hormonal therapy (64%)	8%	39-month overall survival (91.7%)	NA	Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, and Geisel School of Medicine, Hanover, New Hampshire, USA (2000–2019)
The present study	80	Mastectomy (29%) Breast-conserving surgery (71%) Adjuvant chemotherapy (16%) Adjuvant radiation therapy (61%) Adjuvant hormonal therapy (92%)	4%	5-year overall survival (85%) 5-year cancer-specific survival (100%) 5-year disease-free survival (96%)	Acute Toxicity Gr I-II %31 Gr II-V %0 Chronic Toxicity Gr I %11 Gr II-V %0	Ten-center study of the Turkish Society for Radiation Oncology breast cancer study group (2005–2022)

NA: Not available

whole breast radiotherapy and/or boost indications, and accelerated partial breast irradiation (APBI) eligibility etc. issues still await clarification.

5 | CONCLUSION

In conclusion, in light of the knowledge that EPC is a benign oncological breast disease with excellent survival rates, the current study showed that local recurrence was observed less frequently in patients who received RT boost compared to those who did not. The 5-year CSS and DFS of 100% and 96%, respectively, support the favorable clinical prognosis of these tumors. Turkish Society of Radiation Oncology hopes to help better understand this rare type of cancer and aims to shed light on the questions that await answers.

CONFLICT OF INTEREST

The authors have no competing interests to declare that are relevant to the content of this article.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Necla Gurdal, Berna Akkus Yildirim, Ozge Kandemir Gursel, Selnur Ozkurt, Kamuran Ibis, Melis Gultekin, Huseyin Tepetam, Sule Karabulut Gul, , Didem Colpan Oksuz, Ilknur Alsan Cetin, Berrin Yalcin, Mursel Duzova, and Gul Kanyilmaz. The first draft of the manuscript was written by Necla Gurdal, Berna Akkus Yildirim, Guler Yavas, Zeynep Ozsaran, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of Istanbul Prof. Dr. Cemil Taşcıoğlu City Hospital (approval number: E-48670771-514.99).

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How to cite this article: Gurdal N, Yildirim BA, Gursel OK, et al. Oncological outcomes for encapsulated papillary carcinoma of the breast: Multicentric study of Turkish Society for Radiation Oncology breast cancer study group (TROD 06–014 study). *Asia-Pac J Clin Oncol*. 2022;1-10. https://doi.org/10.1111/ajco.13893