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***PTEN* and *PIK3CA* Mutation Positive Breast Neuroendocrine Carcinoma Treated with Molecularly Targeted Therapy Including Capivasertib**

Kyoko Shimoyama¹ and Yoshihiro Ikura²

¹Department of Breast Surgery, Takatsuki General Hospital, Osaka, Japan

²Department of Pathology, Takatsuki General Hospital, Osaka, Japan

Correspondence: Kyoko Shimoyama, Department of Breast Surgery, Takatsuki General Hospital, 1-3-13 Kosobecho, Takatsuki, Osaka, 569-1192, Japan.
e-mail: masumura410@yahoo.co.jp

Case report

**Title: *PTEN* and *PIK3CA* mutation Positive Breast Neuroendocrine Carcinoma
Treated with Molecularly Targeted Therapy Including Capivasertib**

Running Title: BNEC treated with exclusive molecularly targeted therapy

Kyoko Shimoyama^{1*} and Yoshihiro Ikura²

¹Department of Breast Surgery, Takatsuki General Hospital, Osaka, Japan

²Department of Pathology, Takatsuki General Hospital, Osaka, Japan.

Correspondence: Kyoko Shimoyama, Department of Breast Surgery, Takatsuki

General Hospital, 1-3-13 Kosobecho, Takatsuki, Osaka, 569-1192, Japan.

E-mail: masumura410@yahoo.co.jp

Abstract

Breast neuroendocrine carcinoma (BNEC) is rare (<0.1%) but is clinically important due to its rapidly progression, treatment-resistant, and poor prognosis despite being hormone receptors-positive. No effective treatment for BNEC has been established. BNEC is little recognized, so it may be overlooked as an invasive carcinoma of no special type. However, an early diagnosis of BNEC is critical, as it allows for comprehensive genomic profiling (CGP). We present a case of a woman in her 40s with heterochronic bilateral breast cancer, who was ultimately diagnosed with BNEC due to the rapid disease progression with bone, liver, and lung metastases, during semiannual follow-up. CGP revealed *PTEN*, *PIK3CA*, and *ESR1* mutations as well as a high tumor mutational burden (TMB-high). While she received everolimus, abemaciclib, and bevacizumab, capivasertib was most effective. BNEC is rare, but an early diagnosis, based on clinical course, is key for CGP and correct treatment selection.

Keywords: Breast neuroendocrine carcinoma, metastatic breast cancer, Capivasertib, molecularly targeted therapy, *PIK3CA* mutation

Introduction

Breast neuroendocrine carcinoma (BNEC) is a rare cancer ($< 0.1\%$) (Cloyd et al. 2014; Ozaki et al. 2021; Jiang L et al. 2024), characterized by rapid progression, resistance to treatment, and poor prognosis. Approximately 20% of patients are diagnosed with Stage IV, whose median survival is around two months, with a one-year survival rate of about 30% (Cloyd et al. 2014; Xia et al 2023). Compared to the median survival of 44.8 months for typical hormone-positive metastatic breast cancer (Grinda et al. 2021), NEC progresses extremely rapidly, so the conventional treatments cannot be expected to improve prognosis. BNEC itself is an independent adverse prognostic factor for both OS and DSS (Cloyd et al. 2014; Wang et al. 2014). While neuroendocrine carcinoma commonly arises in the gastrointestinal tract and bronchopulmonary system, the mammary tumors are infrequent (Savelli et al. 2012) but show a similar rapid and aggressive course. Accordingly, there's no time to waste on ineffective treatments for patients with BNEC.

BNEC has no particular characteristics on images, and is often hormone-receptor positive (Cloyd et al. 2014; Orelli et al. 2020; Gallo et al 2021; Ozaki et al. 2021; Jiang L et al. 2024). Therefore, BNEC is likely to be diagnosed and treated as either an ordinary type of breast cancer or a small cell lung cancer, primarily by chemotherapy. However, no specific treatment protocol for BNEC has yet been established (Hojo et al. 2009; Boutrid 2020; Xia et al 2023).

As described above, BNEC may lurk among hormone-receptor positive breast cancers with an aggressive clinical course. Although BNEC is rare and under-recognized, an early diagnosis is crucial, because patients diagnosed as having BNEC can immediately be subjects for comprehensive genomic profiling (CGP) as rare cancer patients. This

approach helps to avoid ineffective treatments and enable to select appropriate treatments, such as molecularly targeted therapy and immune checkpoint inhibitors (ICIs), which is usually applicable only for triple-negative breast cancer, but can be used also for hormone-positive breast cancer with a high tumor mutation burden (TMB).

Here we present a case of BNEC that was ultimately diagnosed due to its rapidly progressing clinical course. CGP revealed that capivasertib and ICIs were effective. The patient received exclusive molecularly targeted therapy and hormonal therapy and resulted in relatively long-term survival as BNEC while maintaining QOL without chemotherapy.

Case Presentation

A 40s-year-old woman presented with an asymptomatic mass in the left breast and enlarged axillary lymph nodes detected by mammography and ultrasonography (US) (Fig. 1A and B). Five years prior to the current tumor, she had a contralateral breast tumor, which was diagnosed as invasive carcinoma of no special type (NST) with neuroendocrine differentiation [pT1c N1 M0, Stage IIA; Luminal B type; estrogen receptor (ER) 99%, progesterone receptor (PgR) 99%, HER2 negative, Ki-67 40%, and synaptophysin 30%; Fig. 2]. Following a right mastectomy, she underwent adjuvant chemotherapy (docetaxel and cyclophosphamide) and radiation therapy (RT). As the tumor was hormone receptor positive, she was subsequently managed with hormonal therapy and observed through semi-annual breast US and yearly mammograms. The current left-sided lesions were found by the scheduled examination.

A core needle biopsy was performed on the left breast mass, which was pathologically diagnosed as NST with neuroendocrine differentiation (Luminal B type; ER 95%, PgR 95%, HER2 negative, Ki-67 40% and synaptophysin 95%; Fig. 3). Four months prior to

the detection of the left breast tumor, she experienced temporarily severe cervical pain. Contrast-enhanced computed tomography (CT) was performed to evaluate systemic metastasis, revealing multiple metastases in the lungs, livers and bones (Fig. 1C-E). Axial vertebrae (C2) involvement was detected, which was considered a potential cause of the previous cervical pain. Systematic treatment was initiated immediately to prevent paralysis or sudden death. The patient's treatment regimen was changed from tamoxifen to a combination of everolimus and exemestane. Since the patient refused cervical spine fusion surgery for bone metastases and chemotherapy, we were forced to choose hormonal therapy and molecularly targeted drug treatment. Everolimus was selected because it has been confirmed to be effective against NEC in the lungs and gastrointestinal tract (Yao et al. 2016).

Despite being under tamoxifen administration, the metastases of the typical hormone-positive breast cancer appeared quite rapidly. The pathology was therefore reviewed, and the diagnosis was corrected to BNEC based on the 2019 WHO classification. It was recognized as a heterochronic bilateral breast cancer (cT1cN1cM1, Stage IV) that was independent from the previous right breast cancer because of the substantial differences in the morphological and immunohistochemical findings between the current and previous breast cancers (Figs. 2 and 3). The presence of a suspected *in situ* lesion within the invasive cancer also supports above our understanding (Fig. 3D). Additional genetic testing, immunohistochemical and molecular examinations were performed. The results were all negative for *BRCA1/2* mutations, microsatellite instability (MSI) and HER2 (4B5). She refused additional systemic chemotherapy, preferring to be treated only with molecularly targeted therapy and hormonal therapy. RT and denosumab were initiated to treat bone metastases.

The treatment course and alterations of tumor markers and CT/US findings are shown in Fig. 4. We offered a regional cancer center to carry out CGP for the BNEC, a rare cancer, during the administration of everolimus and exemestane as a first-line therapy. However, the request was refused because the tumor was considered 'typical' NST, not BNEC, at the center. CDK4/6 inhibitor was used as a second-line therapy. Abemaciclib and letrozole were administered, along with RT for bone metastases.

Later, the new release of capivasertib prompted us to offer another institute, a university hospital, to perform CGP again. The hospital agreed to perform CGP (Foundation One CDx) as BNEC. The CGP revealed the presence of the following mutations: *PTEN* loss, *PIK3CA* H1047R, *ESR1* E380Q, *RBI* R320*, *TP53* R280T and *TSC2* D1690fs*27, as well as a high TMB. These indicate that capivasertib and ICIs are effective, but that hormonal therapies other than fulvestrant are not. Given her preference for oral medication over intravenous infusion, capivasertib and fulvestrant were chosen before ICI. Capivasertib was the most effective drug used for this patient, with tumor markers decreased by half levels (Fig. 4). Capivasertib was administered in a total of six courses with dose reductions and temporary discontinuation. During the temporary treatment interruption, due to adverse effects of Grade 2 (fever, eczema, anorexia, diarrhea and vomiting) and Grade 3 (fatigue and malaise), the metastatic liver tumors grew aggressively. The planned treatment was completely discontinued before the administration of ICI due to impaired liver and kidney function. She was transferred to palliative care and maintained a performance status of 1–2 for a month. However, her condition deteriorated rapidly in the final month, and she died 18 months after being diagnosed with BNEC.

Ethical statement

Ethical approval was not required because this report outlines a single case. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Discussion

The present case of BNEC has taught us the following two things. The first is that BNEC may be misdiagnosed as hormone-positive breast cancer that is progressing rapidly. An early clinical suggestion and definitive diagnosis of BNEC are critical for implementing CGP and selecting the optimal treatment. It is essential that both breast surgeons and pathologists recognize this rare type of breast cancer correctly.

Other than being rare and underrecognized, there are three potential reasons why BNEC is difficult to diagnose. One is that BNEC is histologically characterized as a small cell tumor, but it could also be considered a solid type of NST. To prevent the misdiagnosis, it is important that the WHO classification defines BNEC consisting of dense cellular solid nests and/or trabeculae of tumor cells in spindled, plasmacytoid, and polygonal shapes with eosinophilic and granular or clear cytoplasm (Sun et al. 2022). The next possible reason is that approximately 20% of common histologic types of breast cancer exhibit neuroendocrine differentiation (Irelli et al. 2020). Hypercellular mucinous carcinomas and solid papillary carcinomas can also show neuroendocrine differentiation, but they have clearly distinct clinicopathological characteristics from BNEC (Irelli et al. 2020; Ozaki et al. 2021). The most critical reason is that a diagnosis of BNEC requires a positive immunostaining for neuroendocrine markers, such as synaptophysin or

chromogranin A, which is not a routine procedure in breast cancer pathology. As described above, diagnosing BNEC based solely on morphological findings without immunohistochemical results is quite difficult. Even breast cancer specialists may not fully recognize the importance of proper BNEC management based on an accurate diagnosis (Ozaki et al. 2021; Sun et al. 2022).

The second educational point is that using molecularly targeted drugs, such as capivasertib, which is effective against hormone-positive metastatic breast cancer with identified *PIK3CA*, *PTEN* or *AKT1* mutations (Turner et al. 2023), successfully slowed down disease progression, resulting in relatively long-term survival as BNEC while maintaining quality of life (QOL) without chemotherapy.

Because BNEC is rare, there is no optimized treatment protocol. It is often treated similarly to common types of breast cancer or small cell lung cancer, primarily with chemotherapy. Previous review articles have discussed the potential efficacy of everolimus in targeting the PI3K/AKT/mTOR pathway in BNEC. However, there are no reports of its clinical use. In addition, there have been no case reports of patients with BNEC who have been examined with CGP and treated solely with molecularly targeted drugs, such as capivasertib, as in our current case. *PIK3CA* mutations have been reported to be present in 7%-33% of neuroendocrine carcinomas (Boutrid et al, 2020; Irelli et al. 2020; Gallo et al 2021; Ozaki et al. 2021). Our case showed *PIK3CA* mutation as well as *PTEN* loss. Additionally, our case also demonstrated *TP53* gene mutations and *RBI* gene loss in typical neuroendocrine carcinoma. Although everolimus, bevacizumab, and capivasertib were used and showed periodic efficacy, the cancer regrew after withdrawal. Abemaciclib did not result in an obvious therapeutic response, but it may have contributed to slowing down disease progression when combined with RT for bone metastases. The

facts shown in our case suggest that increasing patients tested with CGP could lead to the development of effective treatments for BNEC.

Capivasertib was administered at a reduced dosage, but treatment had to be discontinued due to severe adverse events, accelerating disease progression. If it was used earlier, it could have been more effective. ICIs, which we did not use this time, are considered to be highly effective for cancers with high TMB. A recent report shows that poorly differentiated BNEC has high TMB (Jiang L et al. 2024), which is consistent with our case. If ICIs had been used before capivasertib administration, our patient might have survived for a much longer time. Despite being diagnosed with Stage IV BNEC, our patient achieved relatively long-term survival while maintaining QOL, having been treated only with molecularly targeted therapy and hormonal therapy.

Given the rapid progression and poor prognosis of BNEC, it is also crucial to thoroughly discuss therapeutic strategies and advance care planning with patients at diagnosis.

In conclusion, BNEC may lurk among hormone-receptor-positive breast cancers that show rapid progression. Although BNEC is rare and not well recognized, suspecting BNEC based on the clinical course and making an early diagnosis can lead to the implementation of CGP. Combined treatments with molecularly targeted drugs and hormonal therapy have showed temporary effects, slowing disease progression and resulting in relatively long-term survival while maintaining QOL without chemotherapy.

Further comprehensive studies based on accumulated cases are sought for revealing the pathophysiology of BNEC and establishing effective treatments.

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Author Contributions

Writing - original draft: K Shimoyama, Writing - review & editing: Y Ikura

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Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

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Figure legends:

Fig. 1. Imaging findings at the time of BNEC diagnosis.

(A) Mammography showing an irregular mass at the central in the left breast. (B-1)

Ultrasound showing irregular mass (18x11x10mm) in the left breast and (B-2) lymph nodes (31x21mm) in the left axillary. (C) CT-scan showed multiple lung metastases. (D-1) Contrast CT-scan showed three liver metastases 37mm,21mm, (D-2) and 17mm, (E-1) MRI revealed multiple bone metastases in axial vertebrae and C7, (E-2) L5 and (E-3) CT-scan showed bone metastases in left acetabulum (red arrows).

Fig. 2. Pathological findings in contralateral breast cancer 5 years ago. The pathological diagnosis was NST with neuroendocrine differentiation. (A) Hematoxylin and Eosin (HE) stain. Loupe magnification. (B) HE stain. High power field. (C) Immunoperoxidase stain for synaptophysin. Approximately 30% of tumor cells are positive. Loupe magnification. (D) Immunoperoxidase stain for ER, 95% positive. High power field.

Fig. 3. Pathological findings in this BNEC. (A) HE stain showing infiltrative, densely packed hyperchromatic cells with a high nuclear-to-cytoplasmic ratio. (B) Immunoperoxidase stain for ER, 95% positive. High power field. (C) Immunoperoxidase stain for synaptophysin, 95% positive. High power field. (D) Double immunostain for synaptophysin (red) and p63 (brown). The tumor nests outlined by p63-positive myoepithelial cells (broken circles) are suggested to be an *in situ* lesion. High-power field, further magnified digitally.

Fig. 4. Changes in tumor markers, treatment details, and imaging findings. The black arrow indicated that the tumor markers had been reduced by half levels.

The maximum size of liver metastases was indicated. Liver metastases shrank only once during the first treatment, but continued to grow gradually.

Figure 1

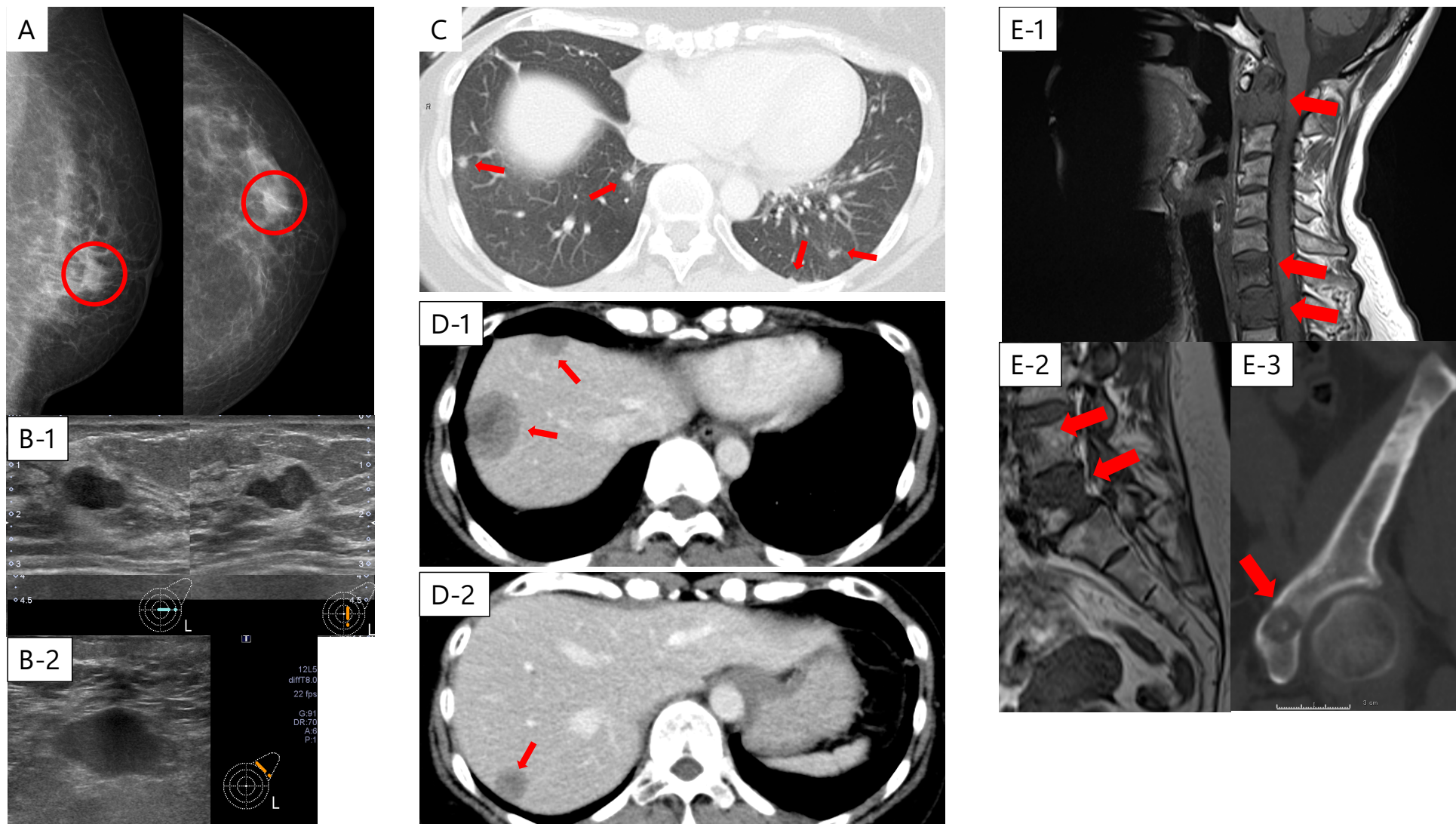


Figure 2

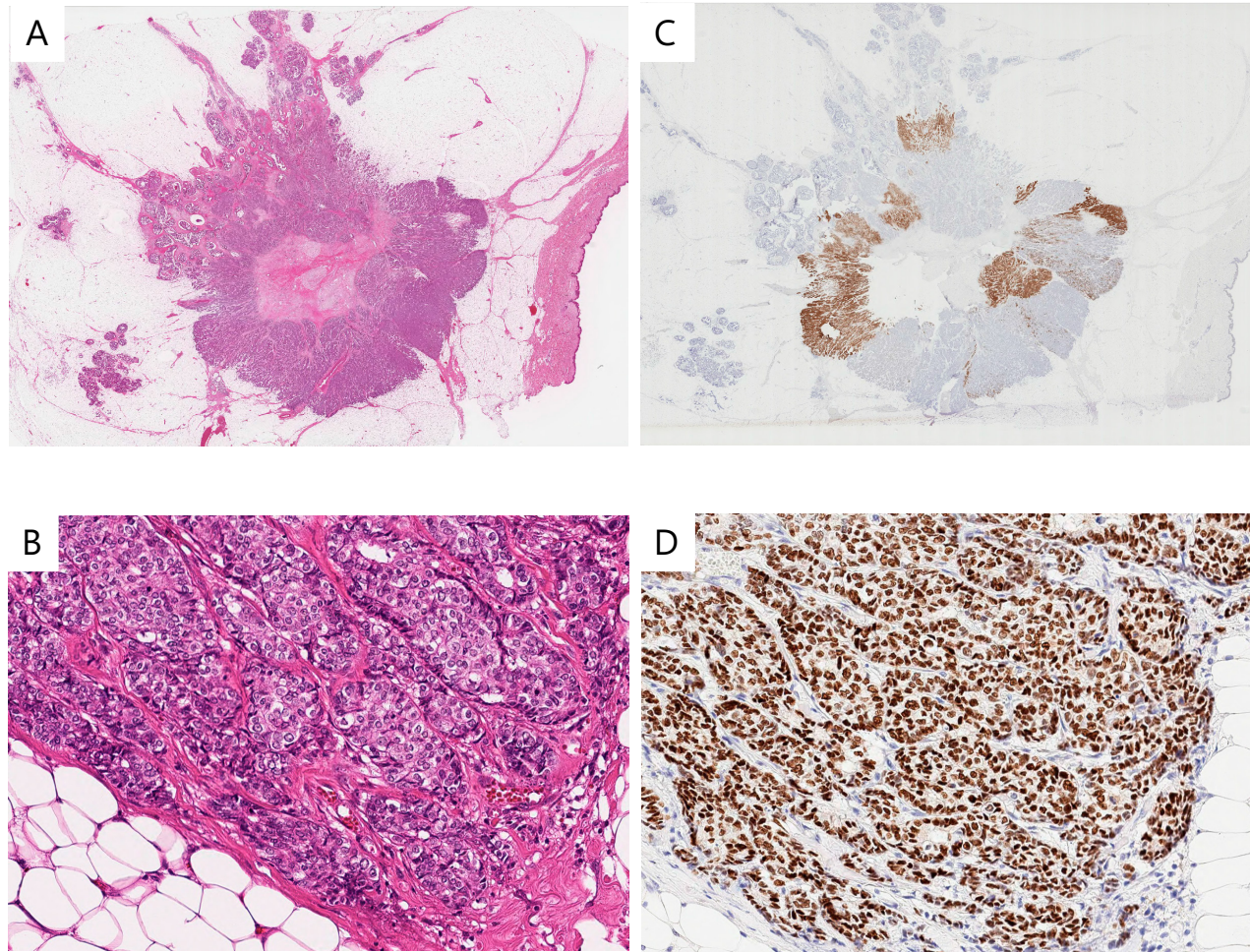


Figure 3

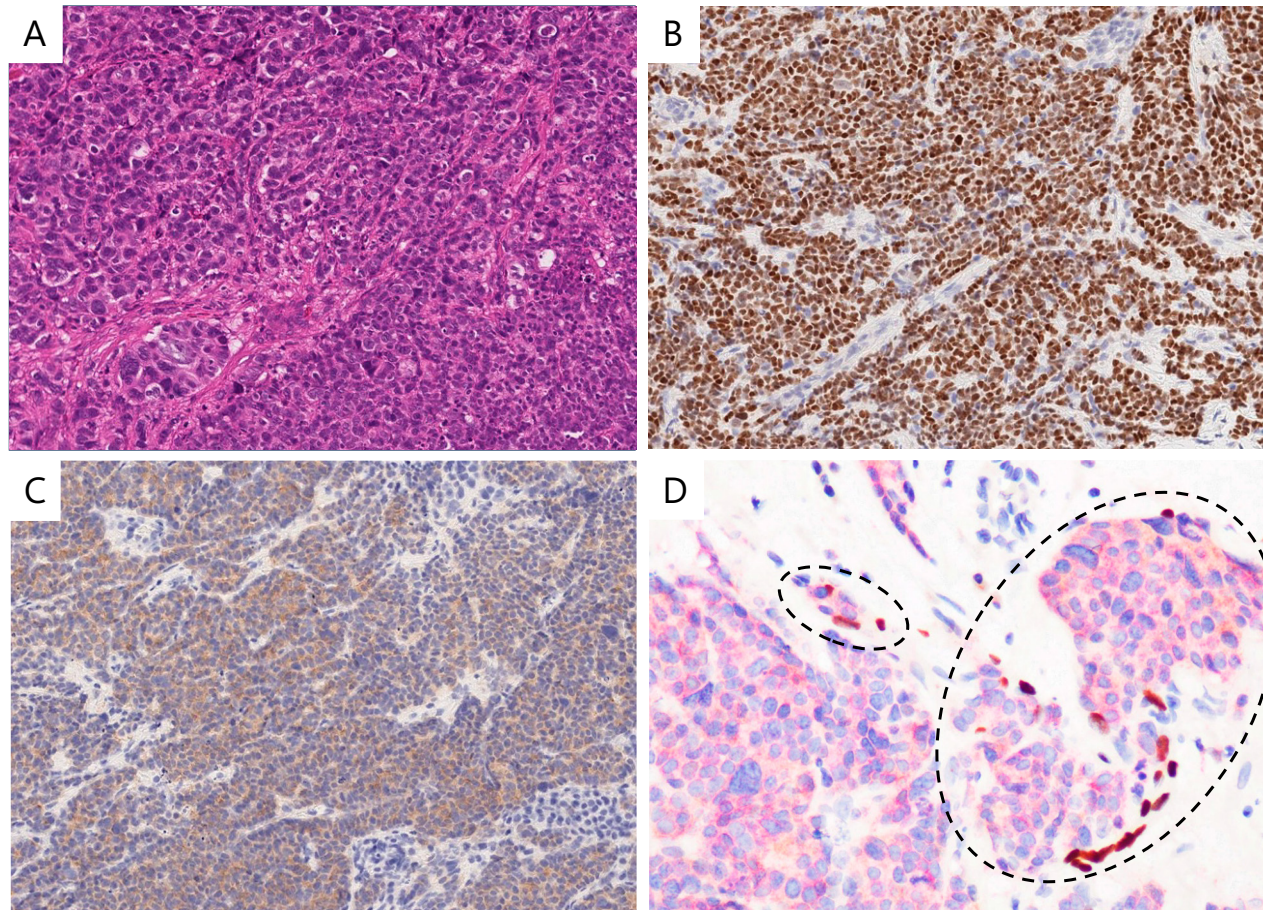


Figure 4

