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Abstract

Purpose:
Breast cancer (BC) is a leading cause of morbidity, disability, and mortality in women, worldwide; triple-negative BC (TNBC) is a subtype traditionally associated with poorer prognosis. TNBC special histology subtypes present distinct clinical and molecular features and sensitivity to antineoplastic treatments. However, no consensus has been defined on the best adjuvant therapy. The aim of the study is to study the evidence from literature to inform the choice of adjuvant treatments in this setting.
Methods:
We systematically searched literature assessing the benefit of adjuvant chemotherapy in patients with TNBC special histotypes (PROSPERO: CRD42020153818).
Results:
We screened 6404 records (15 included). All the studies estimated the benefit of different chemotherapy regimens, in retrospective cohorts (median size: 69 patients (range min–max: 17–5142); median follow-up: 51 months (range: 21–268); mostly in Europe and USA). In patients with early-stage adenoid cystic TNBC, a marginal role of chemotherapy was reported. Similar for apocrine TNBC. Medullary tumors exhibited an intrinsic good prognosis with a limited role of chemotherapy, suggested to be modulated by the presence of tumor-infiltrating lymphocytes. A significant impact of chemotherapy on the overall survival was estimated in patients with metaplastic TNBC. Limitations were related to the retrospective design of all the studies and heterogeneous treatments.

Conclusions:
There is potential opportunity to consider treatment de-escalation and less intense therapies in some patients with early, special histology-type TNBC. International efforts are indispensable to validate prospective clinical decision models.

Keywords (separated by '-') Triple-negative breast cancer - Special histology - Escalation and de-escalation - Adjuvant treatment intensity customization - WHO classification

Footnote Information F. Giugliano, J. Uliano and V.A. Zia have equally contributed to this work.
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REVIEW

Benefit of adjuvant chemotherapy in patients with special histology subtypes of triple-negative breast cancer: a systematic review

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Abstract

Purpose Breast cancer (BC) is a leading cause of morbidity, disability, and mortality in women, worldwide; triple-negative BC (TNBC) is a subtype traditionally associated with poorer prognosis. TNBC special histology subtypes present distinct clinical and molecular features and sensitivity to antineoplastic treatments. However, no consensus has been defined on the best adjuvant therapy. The aim of the study is to study the evidence from literature to inform the choice of adjuvant treatments in this setting.

Methods We systematically searched literature assessing the benefit of adjuvant chemotherapy in patients with TNBC special histotypes (PROSPERO: CRD42020153818).

Results We screened 6404 records (15 included). All the studies estimated the benefit of different chemotherapy regimens, in retrospective cohorts (median size: 69 patients (range min–max: 17–5142); median follow-up: 51 months (range: 21–268); mostly in Europe and USA). In patients with early-stage adenoid cystic TNBC, a marginal role of chemotherapy was reported. Similar for apocrine TNBC. Medullary tumors exhibited an intrinsic good prognosis with a limited role of chemotherapy, suggested to be modulated by the presence of tumor-infiltrating lymphocytes. A significant impact of chemotherapy on the overall survival was estimated in patients with metaplastic TNBC. Limitations were related to the retrospective design of all the studies and heterogeneous treatments.

Conclusions There is potential opportunity to consider treatment de-escalation and less intense therapies in some patients with early, special histology-type TNBC. International efforts are indispensable to validate prospective clinical decision models.

Keywords Triple-negative breast cancer · Special histology · Escalation and de-escalation · Adjuvant treatment intensity customization · WHO classification

Abbreviations

BC	Breast Cancer
DFS	Disease-Free Survival
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
NOS	Not Otherwise Specified
NST	No Special Type
OS	Overall Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TILs	Tumor-Infiltrating Lymphocytes
TNBC	Triple-Negative Breast Cancer
WHO	World Health Organization

F. Giugliano, J. Uliano and V.A. Zia have equally contributed to this work.

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Introduction

Breast cancer is one of the leading causes of morbidity and mortality, worldwide. In 2020, more than 2 million women have been diagnosed with a breast cancer (BC), and 680,000 have died from this disease [1]. The prognosis of BC is determined by clinicopathological and molecular features, and the treatments received [2]. A wide spectrum of histologic entities are encompassed in the definition of invasive BC, the most common being the infiltrating ductal carcinoma of no special type (NST)/ not otherwise specified (NOS), that includes around 75% of all the cases [3] Table 1. The World Health Organization (WHO) has historically systematized the classification of the breast tumors, since 1968, based primarily on pathological criteria and additional ancillary descriptions, as appropriate [3, 4].The histology types described by WHO have a prognostic relevance, as outlined in the Consensus Statement of the College of American Pathologists, since 1999 [5]. WHO has released the fifth edition of the classification of BC, in 2019: eight special types of invasive BC are recognized, along with a group of salivary gland-like tumors, rarer variants of BC and the spectrum of neuroendocrine neoplasms [3] Table 1. In addition, nine histopathology patterns are also described, mostly viewed as part of the spectrum of differentiation of the NOS tumors and not designated as special subtypes per se [3]. Each special variant of invasive BC exhibits distinctive histopathologic features and appears associated with a unique pattern of tumorigenesis and response to chemotherapy [3, 6, 7]. However, clinical decision-making is often informed by limited evidence from small cohorts, anecdotic clinical experience, case reports and expert consensus [8]. Treatment decisions in the setting of early BC are commonly based on clinical, pathological, and molecular features, including the status of the hormone receptors (HR) for estrogen and progesterone, and of the human epidermal growth factor receptor 2 (HER2), ultimately tailored around the single patients' performance status, comorbidities, and preferences [9]. Traditionally, HR- and HER2-negative BC (i.e., triple-negative BC [TNBC]) has been associated with the poorest prognosis along with a more pronounced sensitivity to chemotherapy agents, that is its therapeutic cornerstone all the settings [10]. However, a better characterization of TNBC gene expression profile has revealed a spectrum of tumor entities, each with specific molecular stigmata, prognostic independent significance and variable sensitivity to cytotoxic agents [8, 11–17]. Of note, the landmark studies of TNBC with high-throughput molecular assays have included mainly NOS tumors, therefore providing a description of the heterogeneity of invasive ductal carcinomas rather than an exhaustive representation of the entire TNBC landscape—and of the less common special variants [8]. Of interest, the gene expression profiling of the special types of BC has revealed distinctive repertoires of gene copy number aberrations, when compared to matched NOS tumors [8, 18]. For example, adenoid cystic and secretory carcinomas display recurrent chromosomal translocations with oncogenic transcripts of *MYB* and *NTRK-ETV6*, respectively [19, 20]. Also, metaplastic carcinomas can express high levels of genes commonly described in mesenchymal-like TNBC, enriched in angiogenic gene products [21]. Eventually, some apocrine tumors present a luminal-like gene expression profile related to the androgen hormone stimulation, and segregate in the luminal androgen receptor molecular TNBC subtype [22]. While the prognostic meaning of the special histology and molecular subtypes of TNBC has been reported, the consideration of them into the clinical decision-making in the adjuvant setting is still controversial, and largely based on expert consensus [8]. However, conducting clinical trials specifically designed for rare subtypes might be challenging, due to the small number of cases and would require a substantial effort for the enrollment in an international context. The aim of this systematic review is to better define the benefit of adjuvant chemotherapy in patients with special histology TNBCs and with special histology patterns of NOS BC.

Methodology

We performed a systematic review of the literature on the role of the adjuvant chemotherapy in patients with special histology variants or special patterns of TNBC, interrogating five distinct databases (PubMed, Cochrane, Embase, Web of Science, SCOPUS) [23]. Also, we searched manually all the accessible resources from the meetings of the European Society for Medical Oncology and American Society of Clinical Oncology from 2010, to enhance the research performance; only peer-reviewed material was included. The research question was formulated by using the structured framework PICO, to identify the population, the intervention, the comparison, and the outcome of interest (Supplementary Table 1). The research strategy was developed by the core investigational team (VZ, DT, EF, GC) and shared with all the authors for inputs. We used mapped research terms "breast cancer", "breast tumor*", "breast tumour*", "adjuvant", the histology variants and special patterns as classified by the last version of the WHO Classification of breast tumors [3], the WHO eleventh International Classification of Diseases (ICD) [24] and ICD for Oncology (ICD-O) [25] nomenclatures, and specific MeSH terms, combined with the Boolean operators (Supplementary Table 2), with no

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Table 1 Overview of the principal characteristics of the special types of breast cancer and the special morphological patterns of NST ductal carcinoma

	Variants	Proportion of all breast cancers	Principal clinical features	Key molecular features	Prognostic significance
Special types					
Lobular	Classic Pleomorphic	5–15%	Poor defined breast lump ER-positive, HER2-negative Occurs in women slightly older than NST BC	85% luminal A GEP *CDH-1* loss of function	Controversial if prognosis is better than NST BC
Tubular	–	1.6%	Small size mass; multifocal in 10–20% cases. Spiculated lesion, calcifications variably present at Mx Two-third in post-menopausal women Incidental finding during screening	Luminal A GEP Frequent 16q loss and 1q gain[a]	Excellent prognosis; long-term outcome similar to age-matched women without BC
Cribriform	–	0.4%	Frequently occult, multifocal in 10–20% of cases	Similar to tubular type: luminal A GEP	Favorable outcome, 10y OS rates 90–100%[b]
Mucinous (carcinoma)	Type A (classic) Type B (endocrine)	2%	Well-circumscribed or lobulated mass at Mx, it may mimic a benign lesion Mostly in post-menopausal and elder women	Luminal A gene expression Gene expression pattern similar to NET in type B MC Aberrant DNA methylation of *MUC2*	Low rates of local and distant recurrence, 5y DFS 94% Low or intermediate RS by the 21-gene assay
Mucinous (cystadenocarcinoma)	–	Exceptionally rare[c]	Palpable mass. More common in Asian women	ER, PR-negative, rare HER2-positive cases	Good prognosis, no distant metastasis reported
Invasive micropapillary	–	0.9–2%	Palpable mass, frequently with lymph node metastasis at diagnosis Dense irregular mass with indistinct margins at Mx	Luminal A or B GEP Spectrum of mutations similar to Luminal B NST invasive BC[d]	Worse prognosis than NST BC
Apocrine	–	4%	Firm, poorly circumscribed mass	Steroid receptor profile: ER-negative, PR-negative, AR-positive	Not clear if prognosis is better than NST BC
Metaplastic	Low-grade adenosquamous Fibromatosis-like Spindle cell Squamous cell With heterologous mesenchymal differentiation[g] Mixed[g]	<1%	Palpable breast lump. More likely at advanced stage. Uncommon calcification at Mx[e] >90% lack expression of ER, PR, HER2[f] The majority expresses CK5/6, CK14, p63 and EGFR	Basal-like or claudin low GEP	Fibromatosis-like and low-grade adenosquamous subtypes: more indolent than NST BC High-grade spindle cell, squamous cell, and high-grade adenosquamous carcinomas: worst prognosis Matrix-producing carcinomas: better prognosis

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Table 1 (continued)

	Variants	Proportion of all breast cancers	Principal clinical features	Key molecular features	Prognostic significance
Salivary gland-like and other rare types	Acinic cell	Extremely rare**	Similar to NST BC	Similar to TNBC of conventional histology	Possible intermediate aggressive potential
	Adenoid cystic: • Classic • Solid-basaloid • HG transformation	0.1–3.5%	Elderly women. Unifocal palpable mass Present as TNBC	*MYB* and *MYBL1* rearrangements[h]	Classic AdCC: favorable behavior SB-AdCC and HG-AdCC: worse prognosis
	Secretory	< 0.05%	Slow-growing, firm, painless, mobile mass Indolent clinical course, can mimic a benign lesion at Mx	*ETV6-NTRK3* fusion gene	Good prognosis: 5y OS 94%
	Mucoepidermoid	Extremely rare[h]	Adult women, 29-80y	-	Grading determines the prognosis[j]
	Tall cell with reversed polarity	–	Palpable mass, visible at Mx. Indolent clinical course	*IDH2* p.Arg172 hotspot mutation in 84% of the cases	Good prognosis
Neuroendocrine	NET G1 NET G2 Neuroendocrine Carcinoma Small cell Large cell	< 1% (NET) 0.1% carcinoma	Isolated hard breast lump with or without axillary lymphadenopathy Carcinomas present nodal metastasis more often	Expression of CgA proteins and/or Syn ER and PR expressed in the majority of tumor cells; frequently AR and GCDFP-15-positive Small cell: BCL2-positive, and HER2-negative	Small cell carcinoma is associated with worse prognosis than other NET No data for large cell carcinoma
Histopathology patterns of NST BC[k]					
Medullary pattern	Also reported as a distinct special type of BC	< 5%	Commonly TNBC Peculiar immune cells infiltrate (TILs)	Basal-like GEP *BRCA* mutations	Better outcome than matched TNBC
Oncocytic	–	–	Similar to NST BC Three-quarter expresses ER/PR; a quarter is HER2-positive	Gains of 11q13.1-q13.2 and 19p13	Not conclusive data
Lipid-rich	–	–	–	ER and PR-negative, 50–100% are HER2-positive	Not conclusive data
Glycogen-rich	–	–	Aggressive clinical course in most reports	ER-positive in 35–50% of the cases	Controversial data
Sebaceous	–	–	–	ER, PR, HER2 in 30–60%	Not conclusive data
Neuroendocrine differentiation	–	10–30%[l]	Not different from NST BC	Luminal gene expression profile	Not different from NST BC

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Table 1 (continued)

	Variants	Proportion of all breast cancers	Principal clinical features	Key molecular features	Prognostic significance
With osteoclast-like stromal giant cells	–	0.5–1.2%	Tumors infiltrated with inflammatory cells (derived from monocytes)	–	Same prognosis of NST BC
Chorio-carcinomatous pattern	–	Anecdotical case reports	Tumor cells positive to hCG Women aged 50-70y	–	Insufficient data
Melanotic	–	Anecdotical case reports	Combination of BC and melanoma	–	–
Polymorphous	–	Only 3 cases reported	Palpable nodule. Adult women, 37-74y	–	Insufficient data

Based on the 2019 WHO Classification of breast tumors [3]

AdCC adenoid cystic carcinoma, *AR* androgen receptor, *BC* breast cancer, *BCL2* B-cell lymphoma protein 2, *BRCA* breast cancer gene, *CDH-1* cadherin E gene, *CgA* chromogranin, *CK* cytokeratin, *DFS* disease-free survival, *EGFR* epidermal growth factor receptor, *ER* estrogen receptor, *ETV6 ETS* Variant Transcription Factor 6, *GCDFP*-15 gross cystic disease fluid protein 15, *GEP* gene expression profile, *G1* grade 1, *G2* grade 2, *hCG* human chorionic gonadotropin, *HER2* human epidermal growth factor receptor 2, *HG* high-grade, *IDH2* isocitrate dehydrogenase, *MCs* mucinous carcinoma, *Mx* mammography, *MUC2* mucin 2 gene, *MYB* myeloblastoma proto-oncogene, *MYBL1* MYB-proto-oncogene like 1, *NET* neuroendocrine tumor, *NST* not special type, *NTRK3* Neurotrophic Receptor Tyrosine Kinase 3, *OS* overall survival, *PR* progesterone receptor, *p63* transformation-related protein 63, *RS* recurrence score, *SB-AdCC* solid-basaloid adenoid cystic carcinoma, *Syn* synaptophysin, *TILs* tumor-infiltrating lymphocytes, *TNBC* triple-negative breast carcinoma, *US* ultrasound, *Y* year

**< 50 cases reported

[a]16p gain, loss of 8p, 3p (*FHIT* gene locus) and 11q (*ATM* gene locus) are other recurrent findings

[b]Mixed invasive cribriform carcinoma cancer has less favorable prognosis than pure cribriform type, but better than NST BC

[c] < 30 cases reported

[d]Recurrent gains of 8q, 17q, 20q and deletions of 6q and 13q are reported

[e]Calcifications in metaplastic tumors are observed when associated with in situ cancer and/or osseous differentiation

[f]It can express keratins (epithelial phenotype), SMA, CD10, maspin (myoepithelial markers) but is negative for CD34 and desmin; SMMHC E-cadherin aberrantly expressed within squamous foci; b-catenin may also be aberrantly expressed

[g]A higher number of heterologous morphological components corresponds to an increasingly worse outcome

[h]*MYB-NFIB* fusion gene, *MYBL1* rearrangements, *MYB* amplification

[i] < 40 cases reported. [j]for the mucoepidermoid type, the grading system used for the same tumors originating from the salivary glands can be used

[k]These patterns present the special components (e.g., apocrine foci) in less than 90% of the tumor area

[l]Positive neuroendocrine markers are identified in 20–70% of mucinous and solid papillary tumors

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time restriction, selecting only literature in English language. The research was performed on May 1st, 2020. We run a new research on 5th January 2021, to seek for new studies (none extracted). We included all the studies estimating the benefit of the adjuvant chemotherapy in patients with special-type TNBC; case reports and studies on non-epithelial malignancies were excluded (Supplementary Table 3). Review works and meta-analysis were primarily utilized for snowballing before their exclusion [26]. We did not consider studies on the intrinsic prognostic significance of the histology variants that missed any mention of the adjuvant chemotherapy benefits. The records were double screened by four authors (FG, JU, VZ, DT), through the web app Rayyan (https://rayyan.qcri.org) to manage the screening of the records, in the blind modality; discrepancies in the selection of the papers were discussed as a team, for reconciliation. The lead author (GC) served as a tiebreaker, in case of disagreements. The selection and inclusion process were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary Table 4); the PRISMA flow diagram was used to depict the flow of information throughout the selection, screening, and inclusion phases [27]. (Fig. 1). The data extraction was performed independently by three authors (FG, JU, DT), using an Excel-based spreadsheet (Microsoft®, USA). We extracted information on the histology subtype, study design, the setting of research and the relative timeline; the patient population was characterized per pathological and clinical features and the information on the types of therapies were extracted, including the chemotherapy regimens. For every study, we synthetized the principal findings with a statement on the adjunctive benefit of the adjuvant treatment in that specific subtype of TNBC, based on the single-paper outputs. The research was registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020153818) [28].

Results

Overview

The systematic research of the literature resulted in 6404 unique abstracts screened, of which 15 were included in the final analysis. Table 2. We retrieved original papers on the role of adjuvant chemotherapy for patients with adenoid cystic ($n=1$ papers), medullary ($n=4$), metaplastic ($n=10$, of which 2 on the primary squamous cell of the breast). No eligible study on the special patterns of NOS tumors was identified; in this study, we listed medullary tumors as a special subtype, although currently disputed as part of the spectrum of NOS BCs [3]. All the studies were retrospective, developed in variably sized cohorts of populations (median size: 69 patients; range min–max: 17–5142). No subgroup analysis from clinical trials were reported, and all the studies assessed the correlation between the exposure to chemotherapy regimens and the survival. The patients were enrolled across large timelines (earliest enrollment start period: year 1970; most recent: 2015), with a median follow-up of 51 months (range: 21–268). The studies were conducted in USA ($n=7$), Europe ($n=3$), Asia ($n=3$) and Eastern Mediterranean countries ($n=2$). Table 2. Supplementary Table 5.

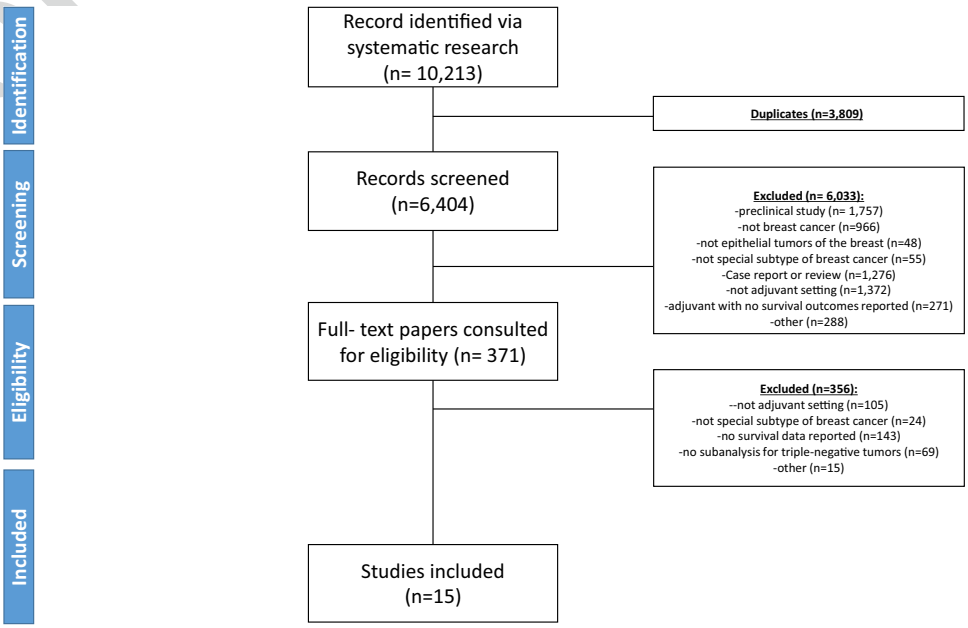

Fig. 1 PRISMA flowchart of the systematic review

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Table 2 Synoptic table of the studies included in the analysis

Histology subtype	Population size	Country (enrollment period)	Stage distribution	Adjuvant chemotherapy type	Survival outcomes	Statement of the benefit of the adjuvant chemotherapy	References
Adenoid cystic	933	USA (1998–2003)	N + (5%)	NA	5y OS: 88%*	Only 11% of patients received ACT, with good prognosis in the overall population	Kulkarni et al. [29]
Medullary	605**	USA (1985–2012)	NA	A, T, non-A	iDFS HR: 0.86 (CI 0.52, 1.41)[a]	Histology did not independently influence iDFS or OS. Tumors with medullary features were associated with better outcomes compared to invasive carcinomas NST on univariate analysis, but this association was lost once TILs were included in a multivariate model	Leon-Ferre et al. [33]
	120	Poland (1970–2005)	Stage I (22%), II (67%), III (12%)	CMF	10y DFS: 90% (N− negative: 93%; N+: 60%)	ACT can probably be safely omitted only in patients with T1 N0 M0 tumors	Stelmach et al. [30]
	26	China (2002–2004)	Stage I & II (96%), III (4%)	CMF, A	OS: 92.3%;	The addition of ACT was associated with a lower relapse rates only in patients with N +[d]	Zhang et al. [31]
	3739	USA (2004–2012)	Stage I (41%), II (52%), III (6%)	A	5y OS: 91.9%; 10y OS: 84.5%	ACT was associated with improved OS in all the population[e]	Mateo et al. [32]

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Table 2 (continued)

Histology subtype	Population size	Country (enrollment period)	Stage distribution	Adjuvant chemotherapy type	Survival outcomes	Statement of the benefit of the adjuvant chemotherapy	References
Metaplastic	69	China (2002–2015)	T1 (15%), T2 (61%), T3 (17%), T4 (7%); N-negative(64%)	CMF, A, T, P	5y DFS: 52.2%; 5y OS: 60.2%	ACT showed to improve the OS in the multivariate analysis, without an impact on DFS[c]	Xiao et al. [34]
	405	UK, The Netherlands, Switzerland, Spain (1991–2012)	T1 (23%), T2 (53%), T3 & T4 (23%)	NA	5y OS: 72%	ACT was associated with longer OS. The benefit appeared to be driven by the subgroup with locally advanced diseases. No impact on DFS	Rakha et al. [35]
	46	USA (1992–2013)	T1 (30%), T2 (44%), T3 (22%), T4 (4%); N + (28%)	A, T	5y OS: 65.3%; 5y DFS: 30%	No impact of ACT on DFS and OS	El Zein et al. [36]
	54	Turkey (1993–2014)	Stage I (16%), II (53%), III (25%)	A, T	3y OS:68%; 3y DFS: 51%	Patients who received T had better PFS and OS	Aydiner et al. [37]
	21	USA (1991–2003)	NA	NA	OS: 71% (CI, 46–96); 5y DFS: 42% (CI, 20–65%)	No impact of the ACT on the survival outcomes	Gibson et al. [38]
	19	Saudi Arabia (1994–2004)	Stage II (42%), III (42%)	A, T, CMF	3y OS: 48%; 3y DFS: 15%	No impact of ACT on the outcomes (DFS, OS)	Al Sayed et al. [39]
	5142	USA (2004–2013)	T1 (32%), T2 (48%), T3 (14%), T4 (5%); N– negative (81%)	NA	5y OS: 56%[b]	ACT was associated with improved OS in the multivariate analysis[f]	Polamraju et al. [40]
	329	USA (2004—2012)	T1 (21%), T2 (44%), T3 (25%), T4 (10%); N– negative (77%)	NA	Median OS: 8.7y; 5y OS: 60%	ACT is associated with improved OS[g]	Kennedy et al. [41]

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Table 2 (continued)

Histology subtype	Population size	Country (enrollment period)	Stage distribution	Adjuvant chemotherapy type	Survival outcomes	Statement of the benefit of the adjuvant chemotherapy	References
Primary SCC of the breast	17	Egypt (1990–2010)	Stage I (18%), II (41%), III (18%), NA (24%)	CMF, A, P/Eto, P/5FU	Median DFS: 24mo (CI: 6.52–41.48); 5y DFS: 29.3%; median OS: 40mo (CI: 20.45–59.55); 5y OS: 39%	ACT showed to improve DFS and OS	Soliman et al. [42]
	29	China (1985–2013)	Stage I (17%), II (45%), III (27%), NA (10%)	CMF, A, T	Median OS: 39mo (7–144 range); 5y OS: 35%	The use of ACT is associated with better survival outcomes[h]	Liu et al. [43]

All the studies are retrospective

A anthracycline-containing regimen, *ACT* adjuvant chemotherapy, *CI* confidence interval 5%-95%, *CMF* chemotherapy containing cyclophosphamide, methotrexate, and 5-fluorouracil, *5FU* 5-fluorouracil, *DFS* disease-free survival, *Eto* etoposide, *mo* months, *HR* hazard ratio, *iDFS* invasive disease-free survival, *N*− lymph node, *N*+ metastatic lymph nodes, *NA* not reported, *NST* not special subtype, *OS* overall survival, *P* platinum-containing regimen, *SCC* squamous cell carcinoma, *T* taxane-containing regimen, *TILs* tumor-infiltrating lymphocytes, *Y* years

*G1 5y OS 91%; Stage 1 5y OS 90%

**This is a mixed cohort of patients: 70% had triple-negative carcinoma of no special type, 16% medullary, 8% metaplastic, and 6% apocrine

[a]Compared to triple-negative tumors NST

[b]5y OS per stage: T1-T2N0 (63.8%), T3-T4N0 (33.1%), T1-4 N + (42.7%)

[c]5-year OS rate: 68.7% Vs 37.2%; HR, 0.27, 95% CI, 0.11–0.67 with and without chemotherapy, respectively

[d]36.8% Vs 66.7% relapse rates with and without chemotherapy, respectively

[e]HR 0.40, CI 0.26–0.62; $P < 0.0005$. This benefit was observed also in the cohort of patients with node-negative tumors

[f]HR without chemotherapy: 1.527; CI, 1.438–1.621; $P < 0.001$

[g]5y OS was 70% in patients receiving ACT Vs 41% without ACT

[h]5y OS: 54% Vs 19%; median OS: 66 vs 28mo; 5y DFS: 45% Vs 13%; median: 77 Vs 15mo

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Adenoid cystic breast cancer

We extracted only one study for the adenoid cystic variant of breast cancer [29]. It is a study based on the Pennsylvania National Cancer Data Base, that enrolled 933 patients with primary breast cancer diagnosed between 1998 and 2008. Tumors presented mostly well-differentiated (grade 1: 46%), with negative axillary lymph nodes (94.9%). Despite being mostly triple-negative breast tumors, the indication for adjuvant chemotherapy was uncommon (11.3%). The study was unpowered to detect a statistically significant difference of the outcome in the patients who had or not received the adjuvant chemotherapy. However, the authors reported a good prognosis both in the overall population (five-year [5y] overall survival [OS]: 88%) and in the subset with well-differentiated or stage 1 tumors (90% and 91% alive at 5y). Therefore, the authors stated for a marginal role of the adjuvant chemotherapy, especially in patients with non-locally advanced adenoid cystic BC.

Medullary breast cancer

Three studies estimated the benefit of adjuvant chemotherapy in patients with medullary-type BC. The first is by Stelmach et al., on a Polish cohort of 120 women with typical medullary-type cancer, of whom only 10 received adjuvant chemotherapy, based on the positive lymph node status at surgery [30]. The authors reported a 10y disease-free survival (DFS) rate of 93% in patients with node-negative disease and untreated with chemotherapy, versus 60% in node-positive and chemotherapy exposed. Therefore, they stated the possibility to omit adjuvant treatments in node-negative patients, based on the different prognosis observed; still, the study was not powered to show a difference in the outcomes related to the chemotherapy exposure. Another study from China on a smaller population ($n = 26$ patients) confirmed the good prognosis in patients with node-negative disease (i.e., OS 92.3%) [31]. However, women who had metastatic lymph nodes and had received chemotherapy, experienced better survival outcomes than patients untreated with systemic adjuvant treatments (OS: 36.8% Vs 66.7% with and without chemotherapy, respectively). A third large study addressed a specific population of patients, presenting with node-negative, 10 to 50 mm sized medullary tumors ($n = 3739$ patients) [32]. In this investigation, Mateo et al. demonstrated a benefit of the adjuvant chemotherapy for tumor > 10 mm (Hazard Ratio [HR] 0.40; 95% confidence interval [CI], 0.26–0.62; $P < 0.0005$), when compared to the patients not treated with adjuvant chemotherapy. A recent study evaluated the benefit of chemotherapy for multiple histology-type ($n = 605$ patients), showing no benefit of chemotherapy in the subset with medullary cancer when the analysis was adjusted for the presence of the tumor-infiltrating lymphocytes (TILs): no histology-type was retained an independent prognostic significance nor informed on the benefit of adjuvant treatments [33]. In this paper, the findings were consistently confirmed when accounting for either intratumoral TILs or stromal TILs. This study also included a subset of patients with *apocrine* breast cancer (6%), for which a role of the adjuvant chemotherapy has not been demonstrated [33].

Metaplastic breast cancer

We analyzed ten papers on the metaplastic BC, of which two specifically for the primary squamous type [34–43]. For the therapeutic approaches reported, we discuss the squamous type as a separate entity. The evidence of an impact of the adjuvant chemotherapy on the survival outcomes was variable. Three smaller studies failed to show a benefit of the chemotherapy in this special type of BC [36, 38, 39]. However, the largest cohorts all reported an association of the adjuvant chemotherapy with an improved OS. A study from China (69 women) showed a benefit of the adjuvant treatment on the 5y OS, reporting a magnitude of benefit of + 31.5% absolute OS gain (HR, 0.27; CI, 0.11–0.67), after adjusting for multiple confounders [34]. A similar magnitude of benefit was reported in a study from USA ($n = 329$ patients) that estimated a 5y OS of 70% and 41% in patients receiving the adjuvant systemic chemotherapy or not, respectively ($P < 0.001$) [41]. The authors of a recent large population-based study from the Texas National Cancer Database confirmed a significant benefit of the chemotherapy in more than five thousand patients with metaplastic BC, with poorer OS in patients untreated with systemic regimens (HR without chemotherapy: 1.527; CI, 1.438–1.621; $P < 0.001$; multivariate model). An impact of the chemotherapy on the DFS was not uniformly confirmed [37]. In particular, only one study suggested a benefit on both DFS and OS, on a cohort of 54 patients from Turkey; however, in this study, the median follow-up time was only 28 months [37]. Our research did not identify any subgroup analysis on the impact of the chemotherapy based on the type of non-glandular metaplastic components of the tumor.

For the *metaplastic squamous cell carcinoma* of the breast, a very rare subtype of metaplastic tumors, we identified two studies [42, 43]. The patients were treated with a combination of therapies often more similar to the ones used in the cutaneous squamous carcinomas, including platinum compounds [42]. Both the studies confirmed a substantial benefit of the adjuvant chemotherapy on the survival outcomes, despite their small patient numerosity. The use of the chemotherapy was associated with an improvement of the 5y OS from 19 to 54%, corresponding to a median OS of 66 months Vs 28 months, and a 5y DFS from 13 to 45% (median DFS: 77 months Vs 15 months) [43].

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Discussion

The management of patients with special histology early TNBC can represent a challenge in the clinical setting, related to the uncertainties on the value of adjuvant chemotherapy. The knowledge of a prognostic significance of the different subtypes is not assurance of a benefit of adjuvant chemotherapy [8]. A better prognosis of TNBC with adenoid cystic, apocrine, and medullary histology has been reported, all experiencing 5y OS rates over 92% and 10y DFS rates over 95%, respectively—when compared to TNBC NOS [8, 44–46]. Conversely, lobular and metaplastic TNBC are associated with the poorest prognosis, with 5y OS rates below 85% [45–48]. A comprehensive review of the impact of the adjuvant chemotherapy in these patients is largely missing, and our study addressed systematically this topic. To our knowledge, this is the first study providing a comprehensive review of the benefit of chemotherapy in special histology of TNBC. The overall incidence of these subtype of breast cancer is around 25%. This number is not insignificant and the clinical decision-making for adjuvant chemotherapy is often challenging in this setting.

In our review we found that adjuvant chemotherapy might have a benefit in patients with more aggressive histology types of TNBC, regardless the stage at diagnosis (e.g., metaplastic tumors), and in case of clinical high-risk presentations of more indolent histotypes (e.g., medullary cancers). For metaplastic tumors, including the primary squamous type, we retrieved the largest chemotherapy benefit, regardless the stage and the lymph node involvement. Conversely, special histology TNBC associated with good prognosis seemed not to derive significant benefits from adjuvant chemotherapy when presenting without lymph node involvement (e.g., adenoid cystic and apocrine TNBC). Notably, medullary tumors seemed to derive some benefits from chemotherapy, including those with negative lymph nodes; however, such a benefit seemed to be affected by the presence of TILs, possibly determining a favorable prognosis and the sensitivity to chemotherapy. The prognostic role of TILs presence, (geo-) spatial organization and immune-population compositions in localized breast cancer has been documented in literature, with a possible predictive role of chemotherapy benefit [49–58]. Therefore, the elucidation of the impact of the immune-infiltrate on the adjuvant therapies represents a priority area to better define the perimeter for effective and safe strategies to de-escalate treatments.

Special histology TNBCs appear primarily chemotherapy-resistant, as reported in the studies with neoadjuvant treatments. One study from Japan enrolled 562 patients with primary BC who had received neoadjuvant chemotherapy between 1998 and 2008 [59]. The investigators reported no tumor shrinkage with chemotherapy in patients with apocrine BC; also, a half of patients with metaplastic TNBC (mostly squamous and spindle cell carcinoma) experienced tumor progression during the treatment, thus displaying a peculiar resistant phenotype. Of note, tumor progression during neoadjuvant chemotherapy is an uncommon event for TNBC NOS, reported in less than 5% of all patients [60]. Accordingly, patients presenting with special TNBC histology types are mostly recommended to upfront surgery and adjuvant therapies, where appropriate, related to the concern of progression during pre-surgical treatments to inoperable tumors and/or over-treatments of more indolent tumor entities [59]. Nevertheless, some authors speculate on the window of opportunity to test ex vivo neoadjuvant therapies in patients with more aggressive TNBC variants, and prompt treatment customization and design molecularly-driven tailored approaches, e.g., post-neoadjuvant therapies [61]. This approach is particularly attractive in window of opportunity clinical trials for patients with special histology TNBC, to identify new therapeutic strategies and for biomarker discovery.

International clinical guidelines for BC management recognize the independent prognostic value of the special types of TNBC [8]. The European Society for Medical Oncology guidelines for the early breast cancer support the 2013 St Gallen recommendations for no systemic therapy for low-risk endocrine non-responsive histology types (i.e., adenoid cystic and apocrine) [63, 64]. The National Comprehensive Cancer Network panel for breast cancer mentions the special types of breast cancer, and argues that some metaplastic tumors are chemotherapy-resistant though indolent in nature, like the *low-grade adenosquamous* and *low-grade fibromatosis-like carcinoma*, having a favorable prognosis without adjuvant chemotherapy [65]. Most recently, the 2019 St Gallen consensus has emphasized that special breast cancer histologies may need different considerations, encouraging the participation to clinical trials and recommending for more research to estimate the clinical magnitude of benefits from adjuvant treatments [9]. A better characterization of biomarkers of treatment response through high-throughput and microarray-based technologies can decode the intrinsic prognostic and predictive nature of the special subtypes of BC and understand how to refine the histological taxonomy [8]. To date, patients with special TNBC-type and high-risk presentations, including those with more indolent entities, should not be denied established adjuvant treatments. Also, the decision for upfront surgery or neoadjuvant therapy should be decided case by case, and not on a rigid operational paradigm. Based on the prognostic information carried by the histology types and the limited evidence on the benefit of adjuvant treatments, there is

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opportunity to discuss a de-escalation of adjuvant chemotherapy, including the omission of systemic treatments, for selected patients with *lymph node-negative tumors, and/or tumors below 10 mm and more indolent TNBCs histologies*. Table 3.

The emergence of biomarkers predictive of benefit from classic and novel adjuvant treatments will play a critical role to refine the clinical decision-making. Accordingly, to understand how the TNBC variants are addressed in the clinical trials, we searched *clinicaltrial.gov (Jan 18th, 2021)*, and rapidly reviewed the ongoing recruiting trials of adjuvant treatments in TNBC ($n = 21$ trials) to understand (i) how the special subtypes are addressed and (ii) what biomarkers are utilized for patient selection. Supplementary Table 6. The ongoing clinical trials mostly test chemotherapy agents alone ($n = 7$) or in combination with immunotherapy ($n = 8$); the most common biomarker utilized for patient selection is the status of pathological response after neoadjuvant therapy ($n = 9$). However, we could not identify any ongoing study that accounted for TNBC special subtypes for selection and stratification. Despite being uncommon entities, the unbalance in the number of special subtypes of TNBC between the arms in clinical trials can possibly undermine the overall data interpretation and, even, jeopardize the results [66]. This is a curious case, because the data collection of clinical trials commonly requires specifying the histology-type and variants of prognostic clinical significance [67]. Therefore, the lack of information on the TNBC subtype can result in a less effective data reporting, and a loss of vital information. Of interest, these omissions have been documented also in HR-positive lobular tumors and seem to broadly affect clinical trials for BC, ultimately depriving essential information to better define effective therapeutic strategies in patients with special histology BC—a non-negligible proportion of all [68].

This research has a number of limitations. Most of the papers report essentially explorative analyses in retrospective cohorts. Patients enrolled had received heterogeneous chemotherapy regimens, including non-standard combinations for BC. For instance, one study showed a better outcome with the addition of taxanes for patients with metaplastic tumors [37], though it was unclear if these patients had received anthracyclines; another study suggested the use of platinum compounds plus etoposide for the squamous variant [42], a non-standard combination for BC; ultimately, these findings should be interpreted as merely explorative and largely speculative—and not *prime time* for the clinical implementation. Also, the cohorts of interest were compared either with TNBC or all-phenotype NST patients, therefore providing different results on the magnitude of benefits, based on the populations selected. Eventually, important prognostic factors like the proliferation index, the grading, lymphovascular invasion were not commonly accounted. Though contemplated in our secondary analysis, we did not identify studies of other adjuvant agents, like hormonal therapies in patients with androgen receptor-positive tumors (e.g., apocrine tumors) or any targeted therapy other than HER2-directed agents [69, 70]. Studies in the metastatic setting have been designed to tailor patients with special type of TNBC, based on recurrent intrinsic molecular features to provide targeted approach, pursuing a histology-molecular continuum—serving as clinical models to select treatments potentially useful in the early setting [71–73].

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Table 3 Operationalization of the findings of the systematic review in the clinical practice and to inform research areas of de-escalation in the adjuvant chemotherapy setting

TNBC histology special type	Clinical setting for chemotherapy de-escalation	LoE	GoR[a]	Research areas for treatment individualization
Adenoid cystic	Stage 1, Grade 1	IV	C	Use of adjuvant androgens modulators; predictive role or TILs
Medullary	T < 10 mm, pN0	IV	C	Predictive role of presence, numerosity and geo-spatial pattern of TILs
Apocrine	pN0	IV	C	Use of adjuvant androgens modulators
Metaplastic, low-grade[b]	pN0	IV	C	Predictive role of the primary tumor dimension on CT benefit
Metaplastic, high-grade	None	IV	C	Treatment intensification and benefit of alternative CT schedules[c]; implementation of window-of-opportunities trials in NAT

LoE and GoR are based on an adaptation for oncology of the Infectious Diseases Society of America-United States Public Health Service Grading System (Dykewicz CA, Clin Infect Dis 2001), in reference to the evidence-recommendations of the adjuvant treatment de-escalation

TNBC triple-negative breast cancer, *LoE* Level of Evidence, *GoR* Grade of Recommendation, *pN0* pathological-negative lymph node, *T* primary tumor dimension, *TILs* tumor-infiltrating lymphocytes, *CT* chemotherapy, *NAT* neoadjuvant treatment setting

[a]For TNBC pT1a (≤ 5 mm) pN0, *adenoid cystic, apocrine,* and *low-grade metaplastic* TNBC, the GoR is B, as per International guidelines for cancer treatment

[b]*Low-grade adenosquamous* and low-*grade fibromatosis-like carcinoma*

[c]It can include platinum compounds in primary *metaplastic squamous* TNBC

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In conclusion, the benefit of adjuvant chemotherapy in patients with special histology TNBC is variable, valuably important in more aggressive special types and negligible in more indolent tumors at earlier stage. The current clinical landscape of clinical trials for adjuvant therapies seems to be insufficient to address the unmet needs of patients with rarer TNBC variants, to inform on the opportunity for adjuvant treatment individualization. This warrants international collaborative efforts to address a non-negligible proportion of patients (~25% of all BC), to validate established prognostic factors and identify innovative biomarkers of patient selection.

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Declarations

Conflict of interest GF, UJ, AM, EF, GV, DT, PD, EA declare no potential COI. GC has received honoraria from Pfizer, Novartis, Lilly, Roche; fees for expert testimony and medical education from Pfizer; and has participated in advisory board s for Pfizer, Roche, Lilly, Novartis, Seattle Genetics, Celltrion. All the declarations are outside the submitted work. CC, received honoraria for speaker bureau, consultancy or advisory role from Roche, Novartis, Pfizer, Eli-Lilly, and MSD. VZ is also employee from Takeda Oncology. No COI in this submitted work.

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