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Viewpoints and debate

Discrepancies between ESMO and NCCN breast cancer guidelines: An appraisal

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ABSTRACT

An ever growing number of medical organizations, societies, working groups and governmental agencies issue algorithms i.e. guidelines, of decision making flowcharts in diagnosis and treatment in a variety of diseases. In the field of evidence-based diagnosis and treatment of breast cancer, a large number of guidelines are available both from medical associations and national health departments. Among the most appreciated and utilized comprehensive guides is the European Society for Medical Oncology (ESMO) Breast Cancer Guidelines and from the other side of the Atlantic the National Comprehensive Cancer Network (NCCN) Guidelines in Breast Cancer. Although there is much concordance between the guidelines from these two organizations, it is intriguing to locate their discrepancies also. The aim of this report is to present a number of different points between ESMO and NCCN in the whole spectrum of breast cancer management, from prevention and diagnosis to treatment and follow up. This systematic review was performed in accordance with the PRISMA guidelines using a predefined search strategy and summarizes in detail, the differences between ESMO and NCCN guidelines regarding genetic risk evaluation and screening, surgery, chemotherapy, endocrine treatment, targeted biological agents, radiotherapy, pregnancy and fertility and follow-up.

Introduction

More than four decades have passed since the conception by Feinstein in 1967 and Cochrane in 1972 on the need for integrating clinical epidemiology tools, such as randomized controlled trials and meta-analyses, into clinical practice [1,2]. The benefit of such a "marriage" is to refine the decision-making process, in order to optimize patient management beyond personal expertise and based on solid evidence. The progeny was Evidence Based Medicine (EBM) in the decade of 1990, a promising discipline that "grew-up" and gave birth to its own offspring, the well-known "Guidelines" [3,4].

An ever growing number of medical societies, working groups and even governmental agencies issue algorithms i.e. guidelines, of decision making flowcharts in diagnosis and treatment in a variety of diseases [5–8]. That is perhaps the current status of maturity of EBM, showing an overwhelming expansion that reflects, at the same time the lack of indisputable evidence in many subjects.

In the field of breast cancer, among the most widely used comprehensive guides is the European Society for Medical Oncology (ESMO) Breast Cancer Guidelines and from the other side of the Atlantic the National Comprehensive Cancer Network (NCCN) Guidelines in Breast Cancer [9,10]. Although there is much concordance between the guidelines from these two

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organizations, it is intriguing to locate their discrepancies also, which we discuss in detail in the current manuscript. It is worth noting the fundamental difference in how the ESMO and NCCN Guidelines are written. The ESMO Guidelines are written as a review, and the reader is required to interpret the summary of data. On the other hand, the NCCN Guidelines are written in algorithmic form with a supporting manuscript that provides the data behind the recommendation. Thus, we had to interpret the implications of the textual data in the ESMO Guideline, but not in the NCCN Guideline.

Materials and methods

This systematic review was performed in accordance with the PRISMA guidelines [11], and has been approved by the Institutional Review Boards of the Alexandra Hospital, Medical University of Athens. For ESMO guidelines, eligible articles were identified by a MEDLINE search up to October 19, 2014. The search strategy included the following keywords: (breast AND (neoplasms OR neoplasm OR cancer OR cancers OR carcinoma OR carcinomas) AND (recommendation [ti] OR recommendations [ti] OR consensus [ti] OR guideline [ti] OR guidelines [ti] OR consultation [ti]) AND ESMO). For the NCCN guidelines, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (www.nccn.org) was searched in order to identify the eligible guidelines.

Two investigators, working independently, searched the literature and extracted data from each eligible study (AT and PL for the section of risk reduction and pre-invasive lesions; HAA Jr. and FZ for the sections of pregnancy and fertility; RB and FZ for the sections of systemic therapy; PL and AT for the sections of surgery and radiotherapy; MAD and GZ for the section of hormonal treatment). In addition, we checked all the references that our search retrieved, so as to identify potentially eligible updated breast cancer-related clinical practice guidelines manuscripts. In instances where multiple (overlapping) publications were identified, the most recent clinical practice guidelines were included. In case of disagreement between the two investigators, team consensus was obtained after consultation with the expert members of the team (HAA Jr, RB, FZ).

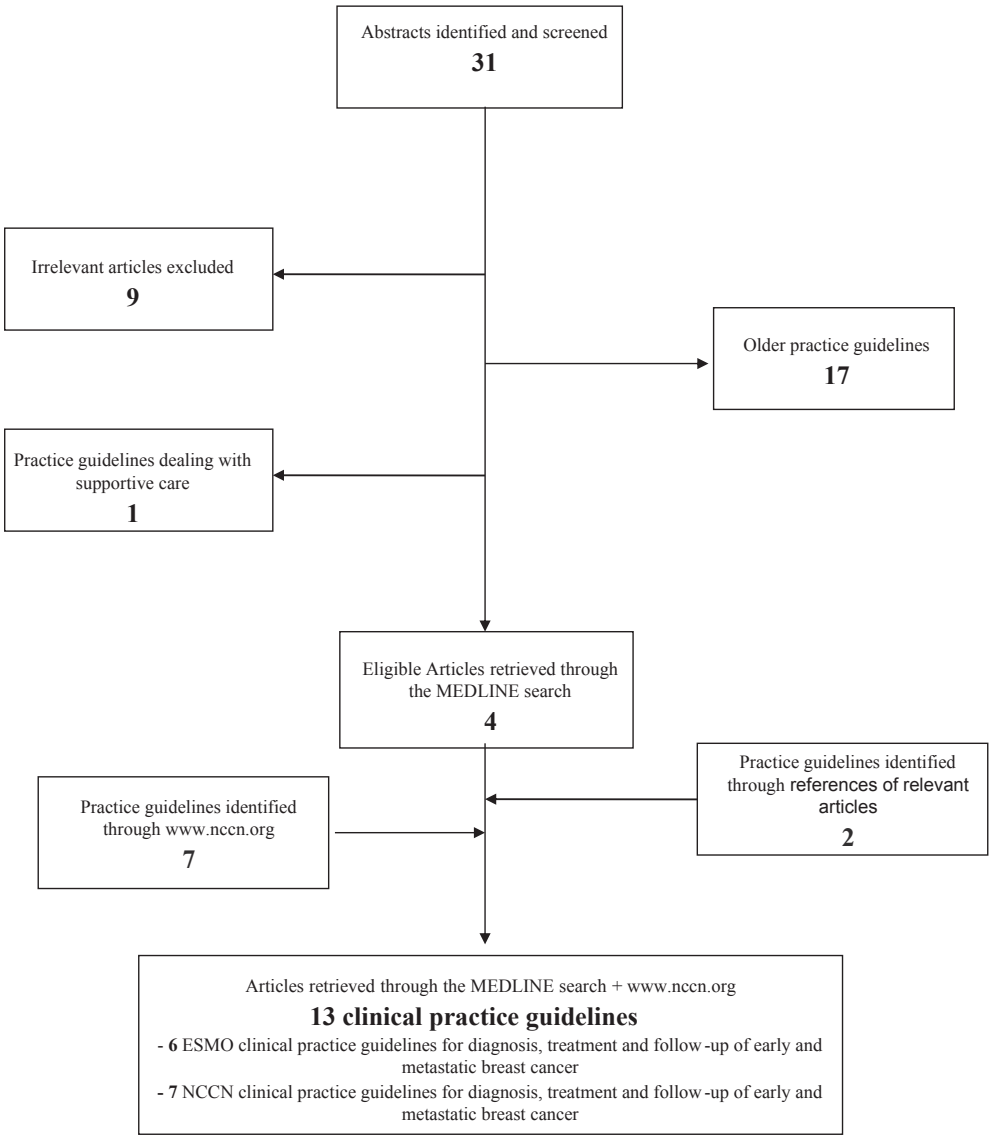

Fig. 1. Stages of the search strategy.

Results

Fig. 1 summarizes the article selection process. A total of six ESMO breast cancer-related clinical practice guidelines were considered eligible [12–17] in addition to seven NCCN clinical practice guidelines namely the following: Breast cancer, Version 3.2014; Breast Cancer Risk Reduction, Version 1.2014; Breast Cancer Screening and Diagnosis, Version 2.2013; Genetic/Familial High-Risk Assessment: Breast AND Ovarian, Version 1.2014; Survivorship, Version 2.2014; Senior Adult Oncology, Version 2.2014; Adolescent and Young Adult (AYA) Oncology, Version 2.2015 [18–24]. The main discrepancies between ESMO and NCCN guidelines are presented in the following sections.

a. Level of evidence and grades of recommendation

The definition of level of evidence and grades of recommendation exhibit some differences between ESMO and NCCN guidelines, which are summarized in Table 1. Of note, within ESMO guidelines, different definitions have been applied.

Table 1
The different definitions on ESMO and NCCN guidelines recommendations.

ESMO		ESO-ESMO (for locally advanced/metastatic setting)	NCCN
Level of evidence			
1A	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analysis of well conducted RCTs without heterogeneity	RCTs without important limitations or overwhelming evidence from observational studies	
1B		RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.	
IC		Observational studies or case series	
2A	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity	RCTs without important limitations or overwhelming evidence from observational studies	
2B		RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
2C		Observational studies or case series	
3	Prospective cohort studies		
4	Retrospective cohort studies or case–control studies		
5	Studies without control group, case reports and expert opinions		
Grade of recommendation			
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended	IA/Strong recommendation, high quality evidence 1 B/Strong recommendation, moderate quality evidence 1 C/Strong recommendation, low quality evidence	(Category 1) Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended	2A/Weak recommendation, high quality evidence 2 B/Weak recommendation, moderate quality evidence 2 C/Weak recommendation, low quality evidence	(Category 2A) Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate (Category 2B) Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…) optional		(Category 3) Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended		
E	Strong evidence against efficacy or adverse outcome, never recommended		

b. Genetic risk evaluation and screening

The major points of discrepancies between ESMO and NCCN recommendations in this field concern the following:

- The onset age of screening and the frequency of routine mammography for unaffected women of average risk
- The need of clinical breast examination complementary to screening routine
- Familial criteria for genetic risk evaluation for unaffected individuals and tumor characteristics for breast cancer patients. We should note that ESMO Clinical Practice Guidelines on "referral for BRCA testing" are not clear as to whether the listed indications relate to relatives or the individual. Presumably they refer to characteristics of the patient's relatives.
- The different gene mutations considered for testing when indicated: ESMO Guidelines limit to considerations of BRCA mutations, while the NCCN Genetic Risk Guidelines consider a broad range of different gene mutations.

Table 2 summarizes in detail, the differences between ESMO and NCCN guidelines regarding genetic risk evaluation and screening.

c. Surgery

The mainstay of breast cancer treatment remains the curative resection of the index tumor along with any involved regional lymph nodes. Yet some points have witnessed controversy with some being a subject of ongoing research:

- The adequate surgical margin after Breast Conservation Surgery (BCS) – Breast- Conserving Therapy (BCT)

Table 2
The differences between ESMO and NCCN guidelines regarding genetic risk evaluation and screening.

	NCCN	ESMO
	Women at average risk	
Clinical breast examination	Clinical breast examination (every 1–3 years) for younger women 25–40 years, of average risk	No statement.
Screening mammography	- Annual Screening mammography - Starts at the age of 40 until 70 at least, unless severe morbidity (upper age limit for screening is not established)	No clear recommendation.
Breast self examination	Optional	Not included in guidelines
	Genetic risk evaluation for unaffected individuals with a family history[a]	
Genetic Risk evaluation for unaffected individuals with a family history of breast/ovarian cancer	- First or second degree blood relative meeting any of the criteria for subjects with personal history of breast cancer. - Third degree blood relative with breast and/or ovarian cancer with >2 close blood relatives with breast cancer (at least one with breast cancer < 50y) and/or ovarian cancer. Significant limitations: - Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patients current age and the age of female unaffected relatives who link the patient with the affected relatives. - Testing of unaffected should only be considered when an appropriate affected member of the family is unavailable for testing	- ≥3 relatives with breast and/or ovarian cancer, with at least one case diagnosed at age <50 or - ≥ 2 breast cancer cases before the age of 40
Genetic Risk evaluation for unaffected individuals with known mutations in the family	A known deleterious mutation in the family	Carriers should be encouraged to advise close family members to obtain genetic counseling.
Genetic Risk evaluation for unaffected individuals with a family history of bilateral breast cancer	Unaffected individuals with a family history of one or more close blood relatives diagnosed with breast cancer ≤50 years. All relatives under age 50 with bilateral breast cancer would meet that criteria, and thus testing would be recommended.	Young onset of bilateral breast cancer
Genetic Risk evaluation for unaffected individuals with a family history of cancers	- ≥ 1 close blood relative with breast cancer diagnosed ≤50 years - ≥ 2 close blood relative with breast cancer diagnosed at any age - ≥ 1 close blood relative with epithelial ovarian cancer - 2 close blood relative with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age.	Breast and ovarian cancer in the same patient
	Genetic risk evaluation for breast cancer patients	
Genetic risk evaluation for an affected individual	- Diagnosed before 45years - Diagnosed before 50 years and have bilateral breast cancer or additional primary (metachronus) or have at least one close relative with breast cancer or have unknown family history - Diagnosed at any age and have a personal history of epithelial ovarian cancer - Personal history of male breast cancer.	Some categories mentioned: - male breast cancer and ovarian cancer or early onset female breast cancer - Ashkenazi Jew with breast cancer of <60 years - young onset bilateral breast cancer - and breast and ovarian cancer in the same patient Genetic counseling should be offered to all adults referred for genetic testing
Genetic risk evaluation for medullary carcinoma	Not mentioned.[b]	Needed
Genetic risk evaluation for triple negative breast cancer patients	Yes; in patients younger than 60 years of age	Only in patients younger than 50 years

[a] ESMO Clinical Practice Guidelines are not clear on "referral for BRCA testing" as to whether the listed indications relate to relatives or the individual. Presumably they refer to characteristics of the patient's relatives.

[b] Medullary breast cancer is essentially always triple negative. The NCCN Guidelines call for testing of individuals with triple negative breast cancer occurring ≤60 years, so any medullary breast cancer in a patient under 60 years would trigger genetic testing per the NCCN Guideline. Medullary breast cancer is also not included in the Breast Cancer Guideline because of the substantial uncertainty whether that histology actually and accurately exists - and the deleterious impact if the histology is falsely diagnosed.

Table 3
The differences between ESMO and NCCN regarding surgical management in the early and metastatic settings.

	NCCN	ESMO
	Carcinoma *in-situ*	
Surgical Margins	In breast conservative surgery, margins < 1 mm are considered inadequate. Close margins (<1 mm) at the fibroglandular boundary of the breast do not mandate re-excision and can be treated with increased boost dose radiation at the involved lumpectomy site.	In breast conservative surgery margins < 2 mm are considered inadequate.
Sentinel lymph node	SLNB recommended in case of pure DCIS treated with mastectomy or with excision in an anatomic location compromising the performance of a future SLNB procedure.	SLNB is recommended in case of large tumors requiring mastectomy and high grade tumors.
Lobular carcinoma ***in-situ*** pleomorphic variant	Some variants of LCIS (pleomorphic LCIS) may have a similar biological behavior to that of DCIS. Clinicians may consider complete excision with negative margins for pleomorphic LCIS, but outcomes data regarding the efficacy of surgical excision to negative margins are lacking. There are no data to support using radiotherapy in this setting.	The pleomorphic variant of LCIS may behave similarly to DCIS and should be treated accordingly.
Paget's disease[a]		
Paget's disease in the absence of invasive or ductal carcinoma.	Surgical therapy includes either mastectomy and axillary staging or excision of NAC with whole breast radiation and +/− boost to NAC sites.	Not mentioned
	Invasive breast cancer	
Contraindications to breast conserving surgery	**Absolute contraindications** to BCT are diffuse suspicious microcalcifiacations, widespread disease and positive pathologic margin. **Relative contraindications** are tumor size >5 cm, prior radiation therapy, active connective tissue disease, focally positive margin and a known or suspected genetic predisposition to breast cancer	Contraindications to BCS are tumor size (relative to breast size), tumor multicentricity, inability to achieve negative surgical margins after multiple resections, prior radiation to chest wall or breast and other contraindications to radiotherapy or patient choice.
Definition of a negative surgical margin	Not defined	No tumor at the inked margin required and a minimum of 1 mm margin preferred for the invasive component.
Preparing tumor bed for radiotherapy	Not defined	Marking the tumor bed with clips to facilitate accurate planning of the radiation boost field where appropriate.
Definition of LABC	Stage IIIA, IIIB, IIIC, IV For stage IIIA with T3N1M0 treatment as for clinical stage I, II can be applied.	Usually, the definition of LABC includes large operable primary breast tumours (stage IIB, IIIA) and/or those involving the skin or chest wall and/or those with extensive lymphadenopathies (stage IIIB, IIIC). We define LABC as inoperable locally advanced disease that has not yet spread to distant sites.
Role of Surgery in LABC after preoperative systemic therapy and no response	Individualized treatment	If LABC remains inoperable after systemic therapy and eventual radiation, 'palliative'mastectomy should not be done, unless the surgery is likely to result in an overall improvement in quality of life.
Role of breast reconstruction in locally advanced disease	Locally advanced breast cancer is not an absolute contraindication for immediate reconstruction and post- mastectomy radiation should be applied regardless of the reconstruction approach (autologous tissue/implant). Exclusion criteria: Inflammatory disease before neoadjuvant therapy and incomplete resolution involvement after neoadjuvant therapy.	For oncological reasons, particularly when post-mastectomy radiation therapy is anticipated, some women will be advised against immediate reconstruction.
Effect of radiotherapy on breast reconstruction	When post-mastectomy radiation is required and autologous tissue reconstruction is planned, it is generally preferred that the radiation therapy precedes the placement of the autologous tissue, because of reported loss in reconstruction cosmesis.	The autologous tissue-based techniques appear to tolerate postoperative RT well.
Effect of smoking and obesity on reconstruction	Smoking and obesity are considered a relative contraindication for breast reconstruction.	Not mentioned
Risk reducing surgery	In Risk Reducing Surgery, total mastectomy with immediate reconstruction is the indicated operation.	Not defined
Indication of NAC sparing mastectomy	NAC- Sparing mastectomy can be considered for early stage, biologically favorable (Nottingham grade 1 or 2, node negative, HER2/neu negative, no lymphovascular invasion) invasive cancers and/or DCIS that are peripherally located in the breast (>2 cm from nipple).	Not mentioned
	Axillary staging	
Managing micrometastasis in the sentinel node	Not mentioned	Axillary treatment does not seem to be required when a sentinel node has micrometastasis (0.2–2 mm).
Level of axillary dissection and minimum number of lymph nodes to be excised	Lymph node dissection should involve level I and II of axillary lymph nodes. Level III dissection to the thoracic inlet should be performed only in cases of gross disease in level II.	Not defined

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Table 3 (*continued*)

	NCCN	ESMO
	At least 10 nodes should be provided for pathologic evaluation to accurately stage the axilla.	
Is there a role for omitting axillary staging in selected patient population?	Staging the axilla may be optional in patients: • with particularly favorable tumors • for whom the selection of adjuvant systemic therapy will not be affected by the results of the staging procedure • elderly • with serious comorbid conditions	Not mentioned
Axillary staging after neoadjuvant systemic therapy	In the preoperative systemic therapy setting the staging strategy is: • SLNB after neoadjuvant treatment when axillary lymph nodes are negative in initial axillary ultrasound and FNA/core biopsy of the suspicious ones. • ALND after neodjuvant treatment when nodes are positive (either in FNA/core biopsy under initial axillary ultrasound or in SLNB done prior or after the neoadjuvant treatment). • Positive lymph nodes must be clipped with detectable marker.	Not defined
	Recurrent and metastatic breast cancer	
Axillary surgery in cases of local recurrence	Axillary lymph node staging is indicated if level I/II axillary dissection was not previously done. In women with previous BCT and SLNB, a repeat SLNB may be technically feasible. Repeat SLNB after mastectomy is discouraged.	Not mentioned.
Role of breast surgery in stage IV disease	It is unclear that women presenting with stage IV disease will benefit from palliative local breast surgery. This local therapy should be considered only after response to initial systemic therapy.	The true value of the removal of the primary tumour in patients with de novo stage IV breast cancer is currently unknown. However, it can be considered in selected patients. Of note, some studies suggest that surgery is only valuable if carried out with the same attention to detail (e.g. attaining clear margins and addressing disease in the axilla) as in patients with early stage disease.

DCIS: ductal carcinoma *in-situ*; LCIS: lobular carcinoma *in-situ*; NAC: Nipple–Areola Complex; BCT: breast conserving therapy; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; FNA: fine needle aspirate; LABC: locally advanced breast cancer.

[a] An extensive discussion of Paget's disease is documented on the NCCN Guideline (it has its own algorithm) while the disease is not mentioned in the ESMO Guidelines.

- The extension of indications of sentinel lymph node biopsy in cases previously considered contraindications, such as multicentric tumors, pregnancy, neoadjuvant therapy etc.
- The optimal surgical treatment of axillary lymph nodes in case of positive sentinel nodes.
- The exact indications and the most appropriate techniques of oncoplastic surgery and breast reconstruction.
- The optimal treatment of recurrent breast cancer.
- The feasibility and usefulness of the resection of the primary tumor in the metastatic setting or even the metastases themselves etc.

Table 3 summarizes the differences between the major European and North American oncology organizations ESMO and NCCN as far as surgical treatment guidelines are concerned, both in the primary and metastatic breast cancer.

c. Chemotherapy, endocrine treatment and targeted biological agents

Cytotoxic chemotherapy plays an important role in the treatment of early breast cancer patients and represents a mainstay of treatment in the metastatic setting. Moreover, biological agents have modified the natural history of breast cancer, improving pCR rates, and providing clinically relevant disease free and in some instances overall survival advantages without significantly compromising quality of life. Hence, they have been increasingly incorporated in standard clinical practice.

Endocrine therapy is indicated in all patients with detectable ER expression, irrespective of the need for chemotherapy and/or targeted therapy. Nevertheless, the plethora of available options frequently makes it very hard to choose the optimal therapy for the individual patient. Here we summarize some of the most important points of debate and continuing research:

- The indications for chemotherapy administration in patients with endocrine sensitive disease.
- The exact role of tumor markers, decision-making tools and gene expression assays. - The need for anthracyclines in the adjuvant setting.
- The duration of chemotherapy and endocrine therapy.
- The use of dose-dense schedules.
- Differences in systematic treatment for elderly patients.
- Differences in systemic treatment of special histological breast cancer subtypes.

Table 4 summarizes the differences between ESMO and NCCN guidelines regarding systemic therapy in the primary, neo-adjuvant and metastatic settings. Of note, the incorporation of novel agents and the differences on indications of chemotherapy administration are the main discrepancies between the two guidelines. The ESMO guidelines appear to give more weight to the biological features of the tumor to determine the need for chemotherapy even in the adjuvant setting, whereas tumor staging emerge as the key factor in the NCCN guidelines.

d. Radiotherapy

Radiotherapy is an integral part of the management of all stages of breast cancer. Several issues regarding the indications of

Table 4
The differences in systemic therapy between the ESMO and NCCN guidelines in adjuvant, neoadjuvant and metastatic settings.

	NCCN	ESMO
	Chemotherapy (adjuvant setting)	
HR-positive/HER2-positive disease	Endocrine therapy only in T1aN0M0 disease; endocrine therapy alone or endocrine therapy plus adjuvant chemotherapy plus trastuzumab in T1apN1miM0 or T1bN0M0 disease; with endocrine therapy plus chemotherapy plus trastuzumab disease in patients with T1-3N0M0 or T1-3NanyM0 disease.	Chemotherapy plus trastuzumab even in patients with T1aN0M0 disease.
HR-positive/HER2-negative disease	-Chemotherapy indicated in node-positive tumors and tumors >0.5 cm with high recurrence score. -Chemotherapy may be considered in tumors ≤0.5 cm and pT1mi and in tumors >0.5 cm with intermediate recurrence score. OncoTypeDx test should be considered in hormone receptor-positive, HER2-negative, node-negative disease, and if not performed then the decision is based upon classic prognostic/predictive features.	Chemotherapy indicated in high-risk steroid receptor positive tumors or luminal-A like tumors with extensive local disease
HR-negative/HER2-positive disease	Chemotherapy plus trastuzumab should be considered for tumors T1apN1miM0 disease and for T1bN0M0 disease.	Chemotherapy plus trastuzumab even in patients with T1aN0M0 disease.
Preferred regimens	*HER2-negative*: Dose-dense AC − Paclitaxel q2w Dose-dense AC − Paclitaxel weekly TC *HER2-positive*: AC − paclitaxel + trastuzumab (+/− pertuzumab) TCH +/− pertuzumab	Anthracycline-based chemotherapy recommended. Addition of taxanes to adjuvant anthracycline-based chemotherapy improves outcome independently of age, nodal status, tumor size, grading, steroid receptor expression. Dose dense schedules should be considered in highly proliferating tumors
Neo-adjuvant setting		
HER2 targeted therapy	Patients with HER2-positive disease should receive trastuzumab plus chemotherapy in the neodjuvant setting. Pertuzumab can be administered additionally in tumours ≥ T2 or node-positive tumours. Pertuzumab can be administered additionally in tumours ≥ T2 or node-positive tumours. If pertuzumab was not administered in the neoadjuvvant setting pertuzumab may be given as additional adjuvant therapy	For HER2-positive disease, concurrent taxane and anti-HER2 therapy is recommended since it increases the rate of pathological complete response. Anthracycline-based chemotherapy should be incorporated in the treatment regimen. No mention for the use of pertuzumab in the neo-adjuvant setting.
Chemotherapy (metastatic setting)		
Indications of chemotherapy	-Steroid receptor negative disease, -Endocrine refractory steroid receptor positive disease -Steroid receptor positive disease with visceral crisis	-Rapidly progressive disease -Proven endocrine resistance
Preferred agents for HER2-negative disease	Doxorubicine, pegylated-liposomale doxorubicine, paclitaxel, capecitabine, gemcitabine, vinorelbine, eribuline	In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, taxanes, and liposomal anthracyclines.
Role of combination chemotherapy	There is no compelling evidence that combination chemotherapy is superior to single-agent treatment	-Rapid clinical progression -Life threatening visceral metastases -Need for rapid symptom and/or disease control
Endocrine therapy (adjuvant- neoadjuvant- metastatic setting)		
Role of ovarian ablation in the adjuvant setting	In premenopausal patients, addition of ovarian ablation to tamoxifen may be considered	Role of ovarian ablation is not yet clarified, especially in patients receiving prior chemotherapy
Role of extended adjuvant therapy in post-menopausal patients	After 2–3 years on tamoxifen, AIs may be administered for up to five years. After five years on tamoxifen, AIs for five years are recommended but tamoxifen for another five years may be considered	Extended adjuvant therapy should be discussed with all patients
Role of endocrine therapy in premenopausal patients with metastatic disease as first line	Patients who relapsed after >1 year of completing adjuvant endocrine therapy, tamoxifen or ovarian ablation/suppression plus endocrine therapy as in postmenopausal women is recommended	For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine therapy is the first choice. The additional endocrine agent should be tamoxifen unless tamoxifen resistance is proven. An aromatase inhibitor is also a viable option, but absolutely mandates the use of ovarian suppression/ablation. Fulvestrant has not been adequately studied in premenopausal women.
Role of endocrine therapy in postmenopausal patients with metastatic disease as first line	Patients who relapse after >1 year of completing adjuvant endocrine therapy, AIs, SERMs or fulvestrant may be used as first-line therapy. A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 months or on non-steroidal AI, or any time on tamoxifen).	Preferred 1st line ET: aromatase inhibitor or tamoxifen, depending on type and duration of adjuvant ET. Fulvestrant HD is also an option. The addition of everolimus to an aromatase inhibitor is a valid option for some postmenopausal patients with disease progression after a non-steroidal aromatase inhibitor.

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Table 4 (*continued*)

	NCCN	ESMO
Male breast cancer		
Male breast cancer	The use of AI is ineffective without concomitant suppression of testicular steroidogenesis	For ER-positive male breast cancer, tamoxifen is the preferred option. For male patients who need to receive an aromatase inhibitor, a concomitant LHRH agonist or orchiectomy is the preferred option. Aromatase inhibitor monotherapy may also be considered, with close monitoring of response.

HR: hormone receptor; AC: doxorubicin, cyclophosphamide; TCH: Docetaxel, carboplatin, trastuzumab; AI: aromatase inhibitor; SERM: selective estrogen receptor modulator; CT: chemotherapy.

radiotherapy and radiation fields as well as the treatment techniques, the dose fractionation, the tissue doses etc. have emerged and are the target of ongoing trials.

Both guidelines refer to indications for standard treatment with whole breast irradiation after BCS, boost radiation to the tumor bed, radiation to the chest wall after mastectomy and regional radiation

Table 5
The main differences between ESMO and NCCN regarding radiotherapy treatment guidelines in the early and advanced settings.

	NCCN	ESMO
	DCIS	
Indication of radiotherapy in low risk patients	Local recurrence risk factors are −palpable mass, large size, high grade, close margins and age<50 years. Radiation can be omitted after lumpectomy if the patient and physician view the individual as “low risk”.	In some patients with low-risk DCIS (tumor size <10 mm, low/intermediate nuclear grade, adequate surgical margins), omitting radiation after excision may be an option.
When to consider boost	Close surgical margins (<1 mm) at the fibroglandular boundary of the breast (skin, chest wall).	Boost can be considered for patients at higher risk for local failure.
Role of radiotherapy in lobular neoplasia	Not needed.	In lobular neoplasia RT is not warranted, perhaps with an exception for the pleomorphic subtype.
Role of radiotherapy in Paget's disease	Excision of the NAC with whole breast radiation and consideration for boost to NAC sites is a treatment option.	Not mentioned.
	Invasive breast cancer	
Role of adjuvant radiotherapy in the elderly	Breast irradiation may be omitted in those 70 years of age or older with estrogen-receptor positive, clinically node negative, T1 tumors that receive adjuvant endocrine therapy.	Not defined.
Indications of boost after BCS	A boost to the tumor bed is recommended in patients at higher risk: <50 years and high grade disease. Focally positive margin in the absence of extensive intraductal component can be treated with a higher radiation boost dose to the tumor bed.	After BCS, boost irradiation is indicated for patients with unfavorable risk factors for local control including age <50, grade 3 tumors, vascular invasion and non-radical tumor excision
Indications of regional radiotherapy	Regional RT to infra- supraclavicular area and internal mammary nodes when 1−3 positive axillary lymph nodes: • If BCS, whole breast RT and strong consideration for regional RT. • If mastectomy, strong consideration for RT to chest wall and regional RT.	Regional RT within the framework of BCT remains indicated for patients with involved lymph nodes (number of nodes not defined). When 1-3 positive axillary lymph nodes after mastectomy and additional risk factors such as young age, vascular invasion and a low number of examined axillary lymph nodes, consideration for post-mastectomy RT (to chest wall).
Indication of PMRT	When tumor >5 cm or positive margins after mastectomy, consideration for chest wall and regional RT.	When T3−T4 tumors independent of the nodal status or positive deep margins PMRT is indicated (regional RT not defined).
Dose of radiotherapy and role of hypofractionation	The breast should receive a dose of 45−50 Gy in 1.8 −2.0 Gy per fraction or 42.5 Gy at 2.66 Gy per fraction. For regional nodal radiation, dose is 50−50.4 Gy given as 1.8−2.0 Gy fraction size (±scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy).	Doses used for local and/or regional adjuvant irradiation have traditionally been 45−50 Gy in 25−28 fractions of 1.8 −2.0 Gy. Advise for careful monitoring, evaluation and comparison of outcomes in patients under shorter fractionation schemes e.g. 15−16 fractions with 2.5−2.67 Gy single dose.
Role of radiotherapy in locally advanced disease	In locally advanced disease, after axillary clearance, regional RT to infra- supraclavicular lymph nodes plus internal mammary nodes (if involved and strong consideration for RT to internal mammary nodes if not clinically involved).	Regional RT remains indicated for patients with involved lymph nodes. (Details not defined).
Role of axillary irradiation	Not defined.	After axillary lymph node dissection, the resected part of the axilla should not be irradiated, except in cases of residual disease after surgery.
Considerations for APBI	Patients who may be suitable for APBI are: − Women 60 years or older who are not carriers of BRCA 1/2 mutation treated with primary surgery for unifocal T1N0 ER-positive cancer. - Histology should be infiltrating ductal or favorable ductal subtype and not associated with EIC or LCIS, and margins should be negative.	APBI might be considered an acceptable treatment option in: - Patients at least 50 years old with unicentric, unifocal, node-negative, non-lobular breast cancer up to 3 cm in size without the presence of an extensive intraductal component or lymphovascular invasion, and with negative margins of at least 2 mm. (Doses not defined).

Table 5 (*continued*)

	NCCN	ESMO
	34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy is prescribed to the tumor bed.	
Sequencing of radiotherapy in relation to adjuvant chemotherapy	Radiation therapy should follow chemotherapy when chemotherapy is indicated.	RT may be delivered safely during trastuzumab, ET and non-anthracycline-based chemotherapy. If chemotherapy and RT are to be used separately, chemotherapy usually precedes RT.
Timing of autologous tissue reconstruction in relation to radiotherapy	When post-mastectomy radiation is required and autologous tissue reconstruction is planned, it is generally preferred that the radiation therapy precedes the placement of the autologous tissue, because of reported loss in reconstruction cosmesis.	The autologous tissue-based techniques appear to tolerate postoperative RT well.
Timing of implant insertion in relation to radiotherapy	When implant reconstruction is used in a patient requiring radiation therapy, tissue expansion should precede radiation therapy while surgery to exchange the tissue expander with the permanent implant can be performed prior or after the radiation therapy.	Not defined.
	Local and regional recurrence	
Role of re-irradiation	In axillary recurrence, RT if possible to chest wall, infra-supra clavicular nodes and axilla (depending on any prior radiation to the area and the risk for late normal tissue toxicities from the sum of the prior and planned radiation courses). In supraclavicular recurrence, RT if possible to chest wall and infra- supra clavicular nodes. In internal mammary nodes recurrence, RT if possible to chest wall, infra- supra clavicular nodes and internal mammary nodes.	For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases. With modern radiotherapy techniques, it is often possible to re-irradiate with full dose without too many side-effects. Details about the site of regional recurrence not defined. In patients who have received prior radiation, chemoradiation can be considered, as the residual tumour should be considered radioresistant unless combined with a potentiating agent, provided that the patient is judged a candidate and can tolerate additional radiation therapy. Trials evaluating the role of hyperthermia in combination with radiotherapy in patients with chest wall recurrences have shown a significant improvement in complete response rates with the addition of hyperthermia, especially in previously irradiated patients.

APBI: accelerated partial breast irradiation; NAC: nipple areola complex; BCSL breast conserving surgery; BCT: breast conserving therapy; RT: radiotherapy; PMRT: post-mastectomy radiotherapy; EIC: extensive intraductal component; LCIS: lobular carcinoma *in-situ*.

to infra-supraclavicular and internal mammary lymph nodes. Newer treatment schedules such as accelerated partial breast irradiation; intraoperative radiotherapy, brachytherapy etc. are being gradually integrated according to the results of clinical trials. Table 5 summarizes the main differences between ESMO and NCCN as far as radiotherapy treatment guidelines for breast cancer are concerned.

e. Pregnancy and fertility

The optimal management of pregnant women with breast cancer is not well established. While the aim remains a benefit for the mother's life, the main concern lies with the effect of the drugs on the developing fetus and potential long-term implications secondary to *in-utero* exposure. Both guidelines support points that were considered debatable in the past like the use of anthracycline-based regimen starting the second trimester and until week35 of gestation in addition to the possibility of performing SLNB using colloid during pregnancy. Nevertheless, there were other aspects that did not witness complete concordance between both guidelines and are summarized in Table 6.

Pregnancy after breast cancer was a subject that was not fully addressed by the NCCN while was discussed at length in the latest ESMO guidelines [14]. NCCN obviously supports the concept of pregnancy following breast cancer as they advocate the feasibility of breastfeeding after breast cancer and also the use of fertility preservation techniques. Both guidelines were largely concordant regarding fertility preservation recommendations for breast cancer patients. They supported the early referral to fertility specialists, the use of oocyte and embryo cryopreservation as the main reliable means of fertility preservation, yet regarded the co-administration of gonadotropic hormone releasing hormone agonists as an unreliable method to preserve fertility.

f. Follow-up

There is no uniformly defined follow-up schedule for breast cancer, either in the early or metastatic setting. Hence, major differences were observed between ESMO and NCCN guidelines regarding the optimal intervals and the proposed laboratory and imaging tests, which are summarized in Table 7.

Discussion

Although there is a substantial concordance between the ESMO and NCCN guidelines, it is obvious that there are several points of discrepancy, especially when more controversial or less evidence-based issues are evaluated. Actually, it seems that the American organization adopts newer therapeutic strategies in a more straightforward fashion while ESMO shows a more conservative approach.

At this point, it should be noted that EBM originated as a philosophical notion because much of clinical practice in the past was drawn upon the experience of generations of practitioners with no valid scientific evidence. However, it didn't remain a theoretical game but transformed to a discrete medical discipline. As a result, guidelines came into the foreground to bridge the gap between scientific research data and clinical practice and have become an

Table 6
The main differences between ESMO and NCCN guidelines in managing breast cancer during pregnancy and pregnancy in breast cancer survivors.

	NCCN	ESMO
	Breast cancer during pregnancy	
Surgery during 1st trimester of pregnancy	Mastectomy is the only surgical choice	Postponement of radiotherapy until delivery in patients subjected to BCS could result in delay of radiotherapy for >6 months, which could increase the risk of local recurrence Hence, thorough discussion should take place between the patient and the multidisciplinary team to discuss the risks and benefits of the different surgical modalities and the timing of radiotherapy in such cases
Delivery at term	Not mentioned	Strongly encouraged
Chemotherapy dose calculation	Not mentioned	Should follow standard procedures outside pregnancy acknowledged the altered pharmacokinetics of some agents during pregnancy
Weekly schedules of chemotherapy	Not mentioned	Encouraged
	Pregnancy diagnosed during anti-cancer treatment	
Duration of contraception while on anti-cancer therapy	Not mentioned	Should be used before starting any systemic therapy up to 3–6 months following last dose
Methods of contraception	Hormone-based birth control are discouraged Available methods include IUD, barrier methods, tubal ligation or vasectomy	Not mentioned
Pregnancy on tamoxifen	Not mentioned	Patient counseling is needed and pregnancy termination could be considered owing to high risk of malformations with 1st trimester exposure
Pregnancy on trastuzumab	Not mentioned	Pregnancy could be allowed to continue provided that treatment is stopped once pregnancy is diagnosed and the patient is informed that recommendations is based on data derived from limited number of patients
	Pregnancy in breast cancer survivors	
Timing	Not mentioned	Timing has no impact on prognosis. Better to consider pregnancy after two years of completion of therapy to allow adequate ovarian recovery and bypassing period of high risk of recurrence
Safety in endocrine sensitive disease	Not mentioned	Safe irrespective of endocrine receptor status
Role of abortion	Not mentioned	Should not be promoted for therapeutic purposes
Impact of breastfeeding on prognosis	Not mentioned	Not detrimental

BCS: breast conserving surgery; IUD: intrauterine device.

integral part of all parts of current patient management. As such, guidelines are meant to be up-to-date, high quality, logical, practical and handy tools for the busy clinician in every day practice, the goal being the optimization of patient outcome with rational and judicious use of means.

Issues considered controversial in the past have been definitely answered and evolved into common practice, such as breast conserving surgery, sentinel lymph node biopsy, hormonal treatment, etc. From this perspective, it is not surprising that most discrepancies between ESMO and NCCN concern topics either pending to be resolved by ongoing research – the gray zone – or lying at the "borders" of current indisputable knowledge.

As new trends always contradict tradition, much criticism has also been exercised against the blind use of guidelines since clinical decision-making is a complex and conscientious process that incorporates besides scientific evidence, clinical wisdom (the experience of the clinician) and patient characteristics (values, preferences, culture, psychological profile etc.) as well. The answer to that criticism is Evidence-Based Practice, the most contemporary aspect of EBM, that combines these three axes of medical decision making (data, experience, patient) recognizing that patient care is always individualized, vigilant and involving probabilities.

Finally, the whole picture becomes more perplexing if the variables of socio-economical, cultural, geographical, racial and even genetic status is considered, rendering the participation of national authorities in the process of guidelines conformation necessary in order to be applicable and truly useful in national levels. By no means, however, should the use of guidelines receive legal character since their role is only clinician-guiding and not legally obligatory.

Table 7
Differences between ESMO and NCCN guidelines regarding the optimal intervals and the proposed laboratory and imaging tests in breast cancer patients.

	NCCN	ESMO
	Early breast cancer	
Intervals of physical examination	Every 4–6 months for 5 years and then every 12 months	Every 3–4 months for the first 2 years, every 6 months from years 3–5 and annually thereafter
Intervals of mammography	Every 12 months	Every 1–2 years
Role of breast MRI	MRI for subpopulations not defined	MRI surveillance for younger patients especially in case of dense breasts and genetic or familial predispositions
Role of laboratory tests	Not recommended	Routine blood tests are usually indicated to follow up patients on endocrine therapy
Role of HRT	Not mentioned	HRT discouraged

MRI: magnetic resonance imaging; HRT: hormone replacement therapy.

Conflict of interest statement

Fedro A. Peccatori and Hatem A. Azim Jr were lead authors on the ESMO cancer and pregnancy guidelines that was evaluated in the current manuscript. The rest of the authors declare no conflict of interest.

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