

Prescriptive appropriateness in early breast cancer staging exams: preliminary investigation about adherence to the guidelines in the clinical practice

Angelo Errico¹, Alessia Di Rito¹, Alessandra Sallustio², Lilia Bardoscia³, Santa Bambace¹, Maurizio Portaluri², Giuseppe Guglielmi^{4,5,6}, Francesco Tramacere²

¹Radiotherapy Unit, “Mons. Dimiccoli” Hospital, Barletta, Italy; ²Radiotherapy Unit, “A. Perrino” Hospital, Brindisi, Italy; ³Radiation Oncology Unit, S. Luca Hospital, Healthcare Company Tuscany Nord Ovest, Lucca, Italy; ⁴Department of Clinical and Experimental Medicine, Foggia University School of Medicine, Foggia, Italy; ⁵Radiology Unit, “Dimiccoli” Hospital, Barletta, Italy; ⁶Radiology Unit, Hospital “Casa Sollievo Della Sofferenza”, San Giovanni Rotondo, Foggia, Italy

To the Editor,

The National Comprehensive Cancer Network (NCCN), as well as guidelines from European Society of Medical Oncology (ESMO) and the Italian Association of Medical Oncology (AIOM) are against the use of advanced imaging for staging of early breast cancer (BC) (1-3).

Despite the aforesaid recommendations, in selected cases health professionals do not adhere to consensus-based guidelines.

We report the results of a retrospective multicentric study evaluating the prescriptive appropriateness of laboratory biomarkers and instrumental imaging in early BC on the basis of the indications of the main BC guidelines (1-3).

A retrospective collection of clinical data of BC patients (type of surgery performed, pTNM disease staging, type and outcome of prescribed staging exams or laboratory markers, specialist doctor who requested the investigations), along with the prescriptive appropriateness of these exams in relation to the published reference guidelines (1-3), was performed in different Apulian Centers between September 2015 and December 2016.

We analyzed data of 147 patients with pathological stage I-II-III according to AJCC-UICC 2010 VII Edition (4). Globally, 22/147 women (14.9%) had advanced pathological stage of disease (IIIA-IIIC). The patients' mean age at diagnosis was 60 years

(range 26-87 years). 136/147 (92.5%) patients were followed in regional centers; only 11/147 (7.5%) in extra-regional centers.

Table 1 shows the clinical characteristics of the patients.

Postoperative imaging was requested by surgeons for 60 (40.8%) patients, by oncologists for 81 (55.1%) patients and by multidisciplinary tumor board (MTB) for 6 (4.1%) patients.

63 patients (43%) received a dosage of more than one laboratory biomarker. First level imaging was requested for 88.4% (chest X-ray) and 93% (abdomen ultrasound - US) patients and for all (6/6 patients) with BC in situ. Regarding the second level staging exams, 57.4% and 40.6% of patients in early stage of BC had been subjected to radionuclide bone scan (RBS) and total body computed tomography (CT), respectively. A positron emission tomography (PET) scan was inappropriately requested in 7/10 patients.

The reason for inappropriate prescription of RBS (Figure 1) for early stage BC was evaluated in 54/94 (57.4%): 48 RBS were requested for patients in stage I-II, pN0 BC, 3 RBS were requested in stage IIA, N1mic BC, and 3 RBS were requested in BC in situ. All exams were negative for distant metastases. 18/94 RBS were prescribed in patients with stage IIB,pN1 BC, in disagreement with guidelines.

In relation to total body CT, an inappropriate prescription for stage I-II,pN0 BC was performed

Table 1. Characteristics of the studied population (n. = 147).

	n.	%		n.	%
Type of surgery			Abdomen US		
No ALND or SLND	4	2.7	No	10	6.8
Mastectomy + ALND	21	14.3	Yes, negative	103	70.1
Mastectomy + SLNB	3	2.0	Yes, positive	0	0.0
Lumpectomy + SLNB	90	61.2	Yes, doubtful	4	2.7
Lumpectomy + ALND	29	19.7	Yes, unknown	30	20.4
			Chest X-ray		
pTNM disease staging			No	17	11.6
(AJCC-UICC 2010 VII Ed.)			Yes, negative	100	68.0
Stage 0	6	4.2	Yes, positive	1	0.7
Stage IA	68	46.2	Yes, doubtful	3	2.0
Stage IB	4	2.7	Yes, unknown	26	17.7
Stage IIA	37	25.2	Total body CT		
Stage IIB	10	6.8	No	115	78.2
Stage IIIA	11	7.5	Yes, negative	29	19.7
Stage IIIB	3	2.0	Yes, positive	1	0.7
Stage IIIC	8	5.4	Yes, doubtful	2	1.4
Stage IV	0	0.0	Bone scan		
			No	53	36.0
Laboratory biomarkers			Yes, negative	93	63.3
CA 15.3	18	12.2	Yes, positive	0	0.0
CEA	1	0.7	Yes, doubtful	0	0.0
TPA	0	0.0	Yes, unknown	1	0.7
CA 15.3 and CEA	42	28.6	PET		
CA 15.3 and TPA	1	0.7	No	137	93.2
All three	1	0.7	Yes, negative	10	6.8
Not detected	84	57.1	Yes, positive	0	0.0
			Yes, doubtful	0	0.0

Legend: ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy

for 13/32 (40.6%) exams. The remaining 19 patients underwent CT in line with recommendations: 11 patients for stage III BC and 8 patients after a borderline result at previous basic imaging (abdomen US and/or chest X-ray). Among them, 29 CT were negative for metastatic disease, only 1 CT was positive and 2 CT exams provided a borderline result. Therefore, only for the last three patients a PET scan would be justified to resolve the radiological doubt. Despite that, 10 patients underwent PET scan.

The inappropriate prescription of PET scan for early stage BC was evaluated in 7/10 (70%) exams: 5 PET scan were performed after negative CT and 2 PET scan were performed as second level imaging instead of CT scan. All 10 PET scan showed negative results.

Although the role of a MTB for BC is to provide a continuous, coordinated, and cost-effective care to the patient (5), only 4.1% of patients included in our survey received postoperative staging by MTB.

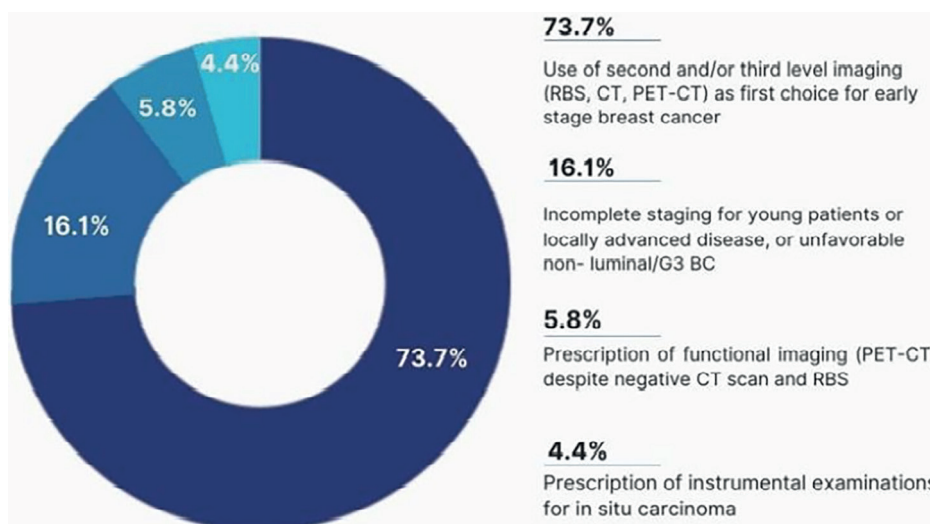


Figure 1. Shows the reasons for inappropriate prescription for second and third level exams.

In 2018, the Puglia region has made mandatory the management of patients diagnosed with BC in the context of a MTB, to optimize the diagnostic and treatment paths. Nowadays, more and more patients are managed inside the MTB and the percentage of staging imaging requested by the MTB has gradually increased. The importance of adherence to guidelines has been remarked by the Regional Council resolution of Puglia region (6), which considered to avoid unnecessary and inappropriate radiological exams that reflect negatively on patients' quality of life and radiation exposure, as well as on the health system's costs.

The principal national and international guidelines used by clinicians involved in BC care have reiterated that routine staging imaging is not indicated for patients with early stage BC in the absence of signs or symptoms of metastatic disease, based on the lack of benefits in early-stage disease (7, 8).

In the study of Puglisi et al (7), distant metastases were identified by RBS in 5.1%, 5.6%, and 14% of patients with stage I, II, and III disease, respectively, and no evidence of metastasis was detected by liver US or chest X-ray in patients with stage I or II disease. A review of Brennan and Houssami (8) confirmed the extremely low prevalence of asymptomatic distant metastases in stage I and II BC (median 0.2% and 1.2% respectively) on the basis of first (chest X-ray

or abdomen US), second (RBS or CT) or third (PET scan) level diagnostic exams.

In our retrospective analysis, 88% and 93% of patients (including all patients with in situ BC) had been subjected, respectively, to inappropriately chest X-ray and abdomen US, and 78% of the total population performed a second or third level exam as the first choice, in contrast with the aforementioned studies. Moreover, 43% of the women received inappropriate requests for laboratory biomarkers, in disagreement with ESMO guidelines (9).

The results of our analysis confirm that during the years 2015-2016, in a considerable number of situations, clinicians didn't adhere to guidelines. The recommendations of the Scientific Societies are realised to optimise patient care, to reduce inappropriate practice variation and to enhance the transition of research into practice (10), but the adherence or compliance by healthcare providers was variable and sometimes sub-optimal. The implementation of the evidences showed by the guidelines into clinical practice is a challenging process. A recent systematic review highlights how barriers to adherence to guidelines can be internal (personal) barriers, as the healthcare provider's knowledge (the lack of familiarity with recommendations, the provider's attitude towards change in the clinical practice, difficulty in the interpretation of guidelines or intentional decisions often based on defensive

medicine's reasons), and external barriers, as the complex nature of a guideline, patient's characteristics (age, comorbidities, quality of life, socioeconomic status), patient's preferences, the environment (i.e. being or not a teaching hospital) (11).

In the next years, a further study will be conducted to collect more recent data from Apulian centers, to evaluate the changes in the prescriptive appropriateness and in the guidelines' adherence after the implementation of the Puglia region resolution (6) inside the Breast Units, and after the regional audits of the MDTs performed at the beginning of year 2022.

Acknowledgements: We would like to thank Doctor Maurizio Portaluri (Head of Radiotherapy Unit, Hospital "Perrino" - Brindisi) and Doctor Santa Bambace (Head of Radiotherapy Unit - Hospital "Mons. Dimiccoli" - Barletta) for the intellectual support in the conceptualization and stylistic review of the article.

Ethic Committee: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hospital "Perrino" - Brindisi on 12th October 2022 (Protocol number 85443/2022). Informed consent was waived because of the use of anonymous clinical data.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author Contribution: Methodology: AE, ADR, AS, FT, GG; Formal analysis and investigation: AE, LB, FT; Writing - original draft preparation: ADR; Writing - review and editing: ADR, AS, AE; Supervision: FT, LB, GG.

References

1. National Comprehensive Cancer Network: NCCN Guidelines: Invasive Breast Cancer V2. 2015.
2. Senkus E, Kyriakides S, Ohno S, et al. ESMO Guidelines Committee. Early Breast Cancer: European Society of Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015 Sep; 26 Suppl 5: v8-30. doi: 10.1093/annonc/mdv298
3. Linee guida AIOM Neoplasie della Mammella Edizione 2015. Available at: http://media.aiom.it/userfiles/files/doc/LG/2015_LG_AIOM_Mammella.pdf
4. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010 Jun;17(6):1471-4. doi: 10.1245/s10434-010-0985-4.
5. Fleissig A, Jenkins V, Catt S, Fallowfield L. Multidisciplinary teams in cancer care: are they effective in the UK? *Lancet Oncol.* 2006; 7(11): 935-943. doi: 10.1016/S1470-2045(06)70940-8
6. Deliberazione della Giunta Regionale 22 maggio 2018, n. 854 che approva la deliberazione del Commissario straordinario dell'A.Re.S.S. n. 32 del 19 febbraio 2018, parte integrante e sostanziale del presente provvedimento. Bollettino Ufficiale della Regione Puglia - n. 85 del 26-6-2018
7. Puglisi F, Follador A, Minisini AM, et al. Baseline staging tests after a new diagnosis of breast cancer: Further evidence of their limited indications. *Ann Oncol.* 2005; 16:263-266. doi: 10.1093/annonc/mdi063
8. Brennan M.E, Houssami N. Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer. *Breast.* 2012; 21:112-123. doi: 10.1016/j.breast.2011.10.005
9. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol.* 2007; 25: 5287-5312. doi: 10.1200/JCO.2007.14.2364
10. Clinical Practice Guidelines We Can Trust (2011) National Academy Press (US), Washington DC. <https://www.ncbi.nlm.nih.gov/books/NBK209546/>. Accessed 31 July 2019.
11. De Guzmán E.N, Song Y, Alonso-Coello P, et al. Healthcare providers' adherence to breast cancer guidelines in Europe: a systematic literature review. *Breast Cancer Res Treat.* 2020 Jun;181(3):499-518. doi: 10.1007/s10549-020-05657-8

Correspondence:

Received: 2 February 2023

Accepted: 25 March 2023

Giuseppe Guglielmi, Professor

Radiology Unit, "Dimiccoli" Hospital, Viale Ippocrate 15
70051 Barletta, Italy

E-mail: giuseppe.guglielmi@unifg.it