

Importance of adherence to guidelines in breast cancer clinical practice. The Italian experience (AIOM)

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ABSTRACT

Aims and background. Project RIGHT (Research for the Identification of the most effective and HIGHly accepted clinical guidelines for cancer Treatment) is promoted by the Italian Association of Medical Oncology (AIOM) to evaluate the concordance between AIOM breast cancer guidelines and clinical practice in Italy. In RIGHT-1, feasibility and the appropriateness of indicators were assessed in patients with early breast cancer. RIGHT-2 evaluated the compliance with guidelines in a nationwide program.

Methods. Thirty-five Italian centers participated in the RIGHT-2 survey. Ten indicators were evaluated to verify an agreement between 2005 AIOM breast cancer guidelines and practice. Patients with clinical stage I-II invasive breast cancer, age ≤ 70 years, who had their first visit at the oncology center between October 2005 and November 2006 were included.

Results. In RIGHT-2, $\geq 90\%$ adherence for the diagnosis indicator and three therapy indicators were observed. The lowest degree of compliance (0%) was observed for the follow-up indicator in asymptomatic patients.

Conclusions. In RIGHT-2, compliance to the 2005 AIOM breast cancer guidelines was 64%. When the follow-up indicator was eliminated, overall adherence to AIOM guidelines was 71%. The results highlight the need to continue improving the already good standards of breast cancer care.

Introduction

Cancer remains a leading cause of mortality especially in developed countries, whereas breast cancer is a major health problem. In Italy, breast cancer represents about 25% of all cases of cancer in women. As a timely diagnosis followed by an appropriate treatment is necessary for a successful outcome, oncology associations need to ensure that patients receive the best possible care. Clinical guidelines are therefore developed and regularly updated by health organizations and clinical oncology associations, whereas surveys are regularly carried out to verify the extent of compliance to such guidelines¹⁻¹⁵. Several factors can influence acceptance and the correct use of guidelines: degree of experience and motivation of physicians, willingness of patients, and availability of resources. According to the recommendations of the Italian National Institute of Health (Istituto Superiore di Sanità)¹⁶, the Italian Association of Medical Oncology (AIOM) in 2002 established a working group to develop clinical guidelines for cancer treatment. The guidelines were first released in 2002 and thereafter have been annually updated. Successively, the RIGHT (Research for the Identification of the most effective and HIGHly accepted clinical guidelines for cancer Treatment) project was created with the aim of evaluating how the guidelines

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had been applied in Italy for the treatment of breast and colon cancers.

In the RIGHT-1 study, the feasibility and the appropriateness of some indicators were assessed in a limited group of patients with breast cancer recruited from a few selected centers¹⁷. This paper reports on the results of the extended survey (RIGHT-2) carried out on many early breast cancer patients from many centers.

Materials and methods

Study design

The RIGHT-2 centers included in the study were randomly selected to be a representative sample of the 319 Italian oncology centers that had been identified in 2003 by AIOM analysis¹⁸. The number of centers needed for the study was calculated on the basis of pilot phase (RIGHT-1) results¹⁷. It was calculated that 42 centers were needed for RIGHT-2 to produce a 95% confidence interval – for the proportion of centers correctly applying the guidelines – equal to 0.75 ± 0.13 . Therefore, centers were extracted from a data base of 319 AIOM centers stratified by geographic area (northern, central, southern Italy, including Sicily and Sardinia) and kind of institution (public hospital, university hospital, research institute, private hospital, other), since these factors were considered to have an important impact on compliance with guidelines.

The number of patients needed for RIGHT-2 was also calculated on the basis of the data provided by RIGHT-1. We calculated that 300 women were needed to observe a proportion of 0.81 ± 0.04 centers applying breast cancer guidelines.

The agreement between clinical practice and 2005 AIOM breast cancer guidelines¹⁹ was evaluated retrospectively on a random sample of medical records. Patients who had their first visit at oncology centers between October 2005 and November 2006 were eligible for RIGHT-2 if they met the following criteria: age ≤ 70 years with clinical stage I or II invasive breast cancer; follow-up by the study center for at least 12 months after diagnosis.

To minimize the response bias, the centers were randomly chosen among all Italian centers associated with AIOM, and the data were retrospectively collected. In addition, the participating centers did not know which indicators were used to assess compliance with guidelines. Monitoring visits were randomly performed at some participating centers in order to ensure a proper data source verification, as well as to correct incongruent or missing data.

Outcome measures

Nine indicators to verify an agreement between guidelines and practice in clinical stage I and II invasive breast cancer were identified by the RIGHT Breast Can-

cer Working Group and then tested on hospital records of breast cancer patients from 11 AIOM centers during the pilot phase (RIGHT-1)¹⁷. Each indicator was accompanied by a multiple choice questionnaire to reveal any reasons for lack of implementation (patient refusal, organizational difficulties or other reasons). The same indicators were used in RIGHT-2, with the addition of a further indicator: proportion of the patients with clinical stage I-II invasive breast cancer undergoing breast-conservation surgery.

Data collection and statistical analysis

Data collection was performed using a web-based interface (each center received a user name and a password for e-CRF). The following data fields were recorded: 1) clinical and demographic characteristics, 2) cancer-related variables such as stage, diagnosis and treatment, 3) waiting times and, 4) care indicators. Onsite monitoring visits were performed at four oncology centers to verify the accuracy of imputed data *versus* medical charts. The principal outcome measure was the proportion of patients following recommended guidelines for each indicator.

To avoid a possible underestimation of agreement percentage, the denominator of each indicator was composed of the “eligible events”, i.e., a subgroup of patients for whom application of the recommended procedures had no contraindications (i.e., co-morbidities and patient decisions). A summary indicator, representing the overall proportion of cases in which guidelines were correctly employed, was also calculated as the ratio between the number of patients who had been treated following guidelines and the total number of eligible patients for each indicator.

Medical records which did not meet the inclusion criteria listed above were excluded from the analysis.

Results

Thirty-five centers participated in this extended phase study (RIGHT-2). The accrual lasted from February to August 2007. The case records of 355 breast cancer patients were examined, and 324 (91%) of these were eligible for the analysis. Among the 31 breast cancer patients excluded from the analysis, 6 (1.7%) were older than 70 years and 14 (3.9%) were not clinical stage I-II or had their first visit to the oncology center outside the period October 2005 to November 2006. Some patients did not satisfy more than one eligibility criteria.

The mean age of the whole population was 52.1 years (SD 8.8), and 137 (42.3%) cases were classified as clinical stage I, 132 (40.7%) as stage clinical IIA, and 55 (17.0%) as clinical stage IIB.

Table 1 reports breast cancer indicators and shows that guidelines were correctly applied in 64% of cases.

Table 1 – RIGHT-2: breast cancer process indicators

Domains	Indicator	Strength of recommendation ^a	Eligible events (n)	Adherence (%)
Diagnosis	Patients undergoing X-ray-mammography	Not reported in guidelines	324	93%
Surgery	Patients with clinical stage I-II undergoing breast-conserving surgery	A	324	74%
Surgery	Patients treated with complete or level I-II axillary dissection	Not reported in guidelines	324	68%
Surgery	Patients with tumor size <3 cm & clinically negative lymph nodes undergoing sentinel lymph node biopsy ^b	Not reported in guidelines	189	57%
Therapy	Patients treated with radiotherapy after breast-conserving surgery	A	238	92%
Therapy	Patients with >5 cm tumor size or ≥4 positive lymph nodes undergoing radiotherapy after mastectomy	B	20	20%
Therapy	Patients starting radiotherapy within 12 weeks of surgery in the absence of adjuvant systemic chemotherapy	Not reported in guidelines	73	43%
Therapy	Patients with positive hormone receptors undergoing adjuvant hormonal therapy	A	294	90%
Therapy	Patients with positive lymph nodes undergoing adjuvant systemic therapy	A	139	100%
Follow-Up	Asymptomatic patients followed-up only by X-ray mammography as diagnostic workup after surgery	Not reported in guidelines	285	0%

^aFrom 2005 AIOM Breast Cancer Guidelines (19).

^b2005 AIOM Breast Cancer Guidelines specified that this procedure must be performed only if adequate facilities and know-how are present in the hospital.

Twenty-two patients did not receive X-ray mammography as a diagnostic procedure. For 14 of these (64%), the clinicians reported that the procedure was not applied because of patient characteristics.

In 84 of 324 patients with clinical stage I-II breast cancer, breast-conserving surgery was not performed due to patient or tumor characteristics (multicentric tumor, micro-calcifications or pregnancy) in 44% of the cases, patient refusal in 5%, technical/organizational reasons in 7%, and other reasons in 15%. Reasons were not reported in 29%.

In 81 of 189 patients with tumor size <3 cm and clinically negative lymph nodes, sentinel lymph node biopsy was not performed due to a lack of appropriate facilities and/or skilled staff (28%), patient decisions or patient characteristics (17%), other reasons (14%), or no available justifications (41%).

An adherence of 90% or more was observed for the indicator “diagnosis” (patients undergoing X-ray mammography) and for three therapy indicators (patients treated with radiotherapy after breast-conserving surgery, patients with positive hormone receptors undergoing adjuvant hormone therapy, and patients with positive lymph nodes undergoing adjuvant systemic therapy). A low degree of compliance in RIGHT-2 was observed for the indicator “radiotherapy after mastectomy in patients with >5 cm tumor or ≥4 positive lymph nodes” (only 20% of enrolled patients had undergone radiotherapy) and for the indicator “patients who had started radiotherapy, in the absence of adjuvant chemotherapy, within 12 weeks of surgery” (only in 43% of these patients was radiotherapy performed within 12 weeks of surgery).

X-ray mammography alone for diagnostic workup after surgery was not performed in any patient, but all underwent numerous diagnostic tests (0% adherence to the follow-up indicator).

Discussion

The RIGHT survey was designed in two phases: RIGHT-1 and RIGHT-2. Results of RIGHT-1 (pilot phase), which tested feasibility and evaluated adherence of the indicators to AIOM breast cancer guidelines at 11 selected oncologic centers, have been previously reported¹⁷. In RIGHT-2, overall adherence to the AIOM guidelines was 64%. When the indicator “follow-up” was not considered (adherence 0%), the overall level of adherence to AIOM guidelines was 71%.

In RIGHT-2, there was an adherence of 90% or more for the following indicators of diagnosis (patients undergoing X-ray mammography) and therapy (patients treated with radiotherapy after breast-conserving surgery, patients with positive hormone receptors undergoing adjuvant hormone therapy, and patients with positive lymph nodes undergoing adjuvant systemic therapy). The low degree of compliance was observed for “radiotherapy after mastectomy in patients with >5 cm tumor or ≥4 positive lymph nodes”: only 4 (20%) of 20 enrolled patients had undergone radiotherapy. This low level of compliance to the guidelines has a limited value due to the small number of patients enrolled. Moreover, 12 of 16 patients who did not receive radiotherapy were treated in oncology centers that lacked radiotherapy facilities.

Furthermore, the proportion of patients who had started radiotherapy in the absence of adjuvant chemotherapy within 12 weeks of surgery was 43%. Among cases with a delay in starting radiotherapy in RIGHT-2, organizational difficulties were given as the reason for delay in 43% of patients. A survey regarding clinical practice in Italy after the conservative treatment of early breast cancer was thus carried out by the Italian Society of Radiation Oncology and reported that the median interval between time of surgery and radiotherapy without chemotherapy was 60 days, with a range of 30 to 180 days. This ample range was due to the fact that currently there are not enough radiotherapy units in Italy to meet demand¹⁴.

Guideline adherence was very low for modality of follow-up in asymptomatic patients. X-ray mammography alone for the diagnostic workup after surgery was not performed in any patient. All patients underwent some diagnostic tests either on the indication of the family doctor or oncologist or on request of the patient herself. The tests included chest radiograph, hepatic echography and bone scan. AIOM guidelines regarding follow-up are based on two well-designed randomized controlled trials published more than 15 years ago, which did not demonstrate any significant survival advantage in the intensive surveillance arms^{20,21}. However, the RIGHT-2 survey showed that in clinical practice these recommendations are not applied at all (adherence to guidelines, 0%). Therefore, it is advisable to rethink the guidelines on follow-up.

Some surveys similar to the RIGHT program have been reported in literature. A population-based study analyzed variations in surgical treatment and guideline compliance with respect to the application of radiotherapy and axillary lymph node dissection, before and after the introduction of sentinel node biopsy (SNB). The study was conducted on 13,532 consecutive surgically treated stage I-III breast cancer patients diagnosed between 1989-2003²². Overall, 41.2% of the patients received breast-conserving surgery (52.1% for a T1 and 26.5% for a T2 tumor, but with marked variations among the hospitals). Of the 5,577 patients who received breast-conserving surgery, 96.5% received radiotherapy, compared to 92% in RIGHT-2. From the year 2000, the proportion of patients receiving an SNB increased and the proportion of patients undergoing an SNB without a subsequent axillary lymph node dissection increased from 1.8% in 1999 to 37.8% in 2002. In the RIGHT-2 survey conducted on 324 patients having clinical stage I-II disease and first visited in the period October 2005-November 2006, the percentage of patients receiving an SNB was higher (57%).

The reason for this could be that RIGHT-2 enrolled a high proportion of patients eligible for SNB (189 of 324 patients had tumor size <3 cm and clinically negative axillary lymph nodes) and was conducted in the period 2005-2006, when SNB was widely utilized compared to

the period 1989-2003 analyzed in the study of Schaapveld *et al.*²²

An Australian prospective longitudinal study conducted on 221 breast cancer patients between 1997 and 1998 using four guideline indicators²³ reported that radiotherapy after conservative breast surgery was administered to 98% of the patients. The result was similar to the 92% observed in RIGHT-2.

In a survey carried out on 71 ASCO member physicians regarding medical oncology practice-based quality measurement²⁴, the only indicator similar to the RIGHT program was "tamoxifen or aromatase inhibitor received for ER-positive or PR-positive patients". Adherence to this indicator was 97% in the survey, comparable to 90% reported in RIGHT-2.

In a retrospective study of 200 new breast cancers diagnosed in 2004, the National Comprehensive Cancer Network (NCCN) guideline compliance rates²⁵ were evaluated for: preoperative evaluation, breast surgery, lymph node surgery, radiation treatment, and systemic adjuvant therapy (87%, 97%, 97%, 77%, and 63%, respectively). The most common reasons for NCCN guideline non-compliance for systemic adjuvant therapy were patient choice for no chemotherapy, advanced age and comorbidities with limited life expectancy. The most common causes for noncompliance to 2004 NCCN radiation therapy guidelines resulted from the use of partial breast radiation after lumpectomy, patient refusal to undergo recommended radiation, and the selective omission of radiotherapy for lumpectomy patients. These results highlight that the investigation of quality breast cancer care requires both measurement of compliance and a careful assessment of the reasons for guideline noncompliance. A review that analyzes only a percentage of compliance may penalize institutions that practice informed consent detailing absolute risks of survival with and without systemic therapy, those that practice evidence-based medicine before the standardized guidelines are updated, and those that treat patients with limited life expectancy from advanced age and comorbidities.

Caution needs to be exercised when analyzing data from the literature, because the indicators, stage of disease, as well as approaches to breast cancer treatment could differ among the various surveys.

Conclusions

The results of the RIGHT-2 survey, conducted in 35 Italian oncology centers, showed that overall compliance to the AIOM breast cancer guidelines was 64%. When the follow-up indicator was eliminated (adherence 0%), the overall adherence to AIOM guidelines was 71%. Such results highlight the need to continue improving the already good standards of breast cancer care. It is also necessary to correctly evaluate adherence to guidelines, as such data would produce an important

contribution to successfully update AIOM guidelines as well as allow for a better planning of future health care interventions by governments.

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