Taking into Account the Complementarity of Contemporary Breast Cancer Guidelines to Leverage Decision Support in the DESIREE Project

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Abstract. Breast cancer is one of the most common cancers in Western countries and the first cause of death among women in France. Studies have reported that the compliance of the treatment with breast cancer clinical practice guidelines (CPGs) is accompanied with a significant improvement of recurrence-free survival and overall survival rates. However, compliance of multidisciplinary tumour board decisions with CPGs remains non-satisfactory. The European project DESIREE aims at building a software package to support the guideline-based management of breast cancer patients. The aim is to select multiple relevant contemporary CPGs published on the management of breast cancer and to concurrently apply them to benefit of the complementarity of the recommendations issued, and leverage the guideline-based decision support. We used a clinical case to compare NCCN and ESMO CPGs in terms of concordance, complementarity, and conflicts. Out of the 757 decision rules extracted from both CPGs, 64 rules were triggered (32 from NCCN, and 32 from ESMO) by the clinical case. Ten rules were concordant, 52 complementary, and two conflicting. Complementarity relies on the different levels of granularity of the IF-parts of the rules that lead to different specific THEN-parts. Another type of complementarity comes from the provision of specific care apart from the breast cancer therapeutic management. The few inter- and intra-CPGs conflicts show the limits of CPGs in particular situations still debated by medical research.

Keywords. Clinical Practice Guidelines, Decision Support Systems, Decision Rules, Breast Cancer

1. Introduction

With nearly 1.7 million new cases diagnosed in 2012, breast cancer is the most common cancer in women worldwide. It is one of the cancers with the best survival rates at five and 10 years (87%, resp. 76%). However, margins for improvement are both possible and necessary (especially for triple-negative and HER2+ breast cancers). Clinical practice guidelines (CPGs) are developed as best evidence-based recommendations for the management of patients with specific conditions. Studies

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have reported that guideline-conforming treatment for breast cancer patients is accompanied with significant advantages in terms of recurrence-free survival and overall survival rates [1]. However, practice variations are still observed with unsatisfactory rates of compliance with CPGs [2].

Clinical decision support systems (CDSSs) that provide patient-specific recommendations do have the potential to improve the compliance of physician decisions with CPGs [3]. However, the choice of the guidelines to be selected as the resources for the knowledge bases of CDSSs is not so easy. Indeed, a large number of guidelines are available in the field of evidence-based diagnosis and treatment of breast cancer. Since guideline authors interpret the available evidence and include their expertise to formulate the recommendations, contemporary breast cancer CPGs, although published on the same topic and at the same period, are quite different in length, structure, and content. The US National Comprehensive Cancer Network (NCCN) Guidelines for Breast Cancer and the European Society for Medical Oncology (ESMO) Breast Cancer Guidelines are among the most utilized comprehensive guidelines. Although there is a substantial concordance between NCCN and ESMO CPGS, Zagouri et al. [4] evidenced several points of discrepancy.

Different CDSSs have been developed to support the decision of multidisciplinary tumour board (MTB) decisions for breast cancer patients [5], but few have been actually routinely used, e.g. OncoDoc [6]. DESIREE is a European-funded project which aims at developing a web-based software ecosystem for the personalized, collaborative, and multidisciplinary management of breast cancer MTBs. DESIREE offers guideline-based, case-based, and experience-based decision support. The work described in this paper concerns the guideline-based decision support system of DESIREE (GL-DSS). The principle is to select multiple relevant contemporary CPGs published on the management of breast cancer and to concurrently apply them to leverage the GL-DSS on the basis of the complementarity of the recommendations issued by CPGs. We defined and assessed the concordance, complementarity, and conflicts attached to the recommended actions issued by both NCCN and ESMO CPGs. The method is exemplified on a case study.

2. Methods

2.1. Materials

NCCN CPGs are described in a comprehensive document of 199 pages, 75 pages of "blocks" describing decisional algorithms, and 124 pages of narrative guidelines. ESMO CPGs are described in an article of 23 textual pages including two decision trees and eight synthetic tables.

Five scenarios have been defined within the DESIREE consortium to characterize the patient management stage along the breast cancer clinical pathway:

- Scenario A: After Diagnosis – Treatment has not started
- Scenario B: After Neo-adjuvant Therapy – No surgery
- Scenario C: After surgery – After Neo-adjuvant Therapy
- Scenario D: After surgery – No Neo-adjuvant Therapy
- Scenario E: After surgery – Incomplete Adjuvant Therapy

2.2. Methods

Once CPGs have been selected, the difficulty for their implementation in CDSSs comes from their translation into a computer-executable format. This task is usually manually performed although natural language processing techniques have proposed methods to semi-automatically formalize the content of narrative CPGs [7]. Like in the DeGeL method [8], NCCN and ESMO CPGs have been first manually structured as semi-formalized human-readable decision rules: "IF [Clinical_Profile] THEN [Actions] [Recommendation_Level] WITH [Grade]". Clinical profiles are defined as a conjunction of criteria: Clinical_Profile = C_1 AND C_2 ... AND C_n. Actions are described as ordered care plans: Actions = T_1 AND T_2 ... AND T_m. The Recommendation_Level describes if the Action is "mandatory", "recommended", "possible", "not recommended", or "forbidden". We have for instance, from NCCN CPGs: "IF Stage I AND No_Clinical_Axillary_Lymph_Node THEN Sentinel_Lymph_Node_Biopsy Recommended WITH NCCN Cat. IIA".

We used Shiffman's method [10] to build the decision rules. From the blocks, tables, decision trees, and the narrative part of CPGs, we performed the atomization step to identify the useful concepts, the de-abstraction step to provide quantitative definitions when notions were qualitatively mentioned, and the disambiguation step (including vocabulary normalization) to identify criteria C_i and cares T_j. The completion step was not performed because as opposed to both case-based reasoning and experience-based reasoning processes that offer solutions to manage the knowledge gaps of CPGs in the DESIREE project, guideline-based decision support is expected to only rely on evidence-based guidelines.

To compare NCCN and ESMO CPGs, we have defined "concordant" recommendations, when identical or similar Clinical_Profiles provide identical Actions, "complementary" recommendations, when identical or similar Clinical_Profiles provide different Actions that could be added without conflict or when Clinical_Profiles uncovered by one guideline are covered by the other and provide recommendations, and "conflicting" recommendations, when identical or similar Clinical_Profiles provide opposite or contradictory Actions that cannot be added.

The method is demonstrated on the clinical case of a patient, aged 71, breast size 90C, no wish for breast conservation, with a nodule of 25 mm and no clinical axillary lymph nodes. The nodule is confirmed by the mammography (ACR5) and ultrasounds (no axillary lymph node). The pathology of the nodule is a ductal invasive carcinoma, ER= 95%, PR=90%, SBR 3, KI67=30%, HER2=1+. The tumour is classified as cT2N0M0 i.e. Stage IIA. The decision of the MTB is to perform a lumpectomy with a sentinel lymph node biopsy (SLNB) followed by a whole breast irradiation. After surgery, the initial histology is confirmed, there are negative margins, and two negative lymph nodes. The patient case is discussed in two TMBs, first to establish the initial treatment (Scenario A) and the second to establish the adjuvant treatment after surgery and no neo-adjuvant therapy (Scenario D).

3. Results

We have built 519 decision rules from NCCN CPGs among which 114 in the Scenario A and 113 in the Scenario D. ESMO CPGs produced 238 decision rules, 75 in the Scenario A and 92 in the Scenario D. The first decision (Scenario A) of the clinical

case triggered 12 NCCN rules and 5 ESMO rules. The second decision (Scenario D) of the clinical case triggered 20 NCCN rules and 27 ESMO rules.

For the Scenario A, there were four concordant rules (2 + 2), 11 complementary rules (9 from NCCN and 2 from ESMO) and two conflicting rules (cf. Table 1). Gathering the different recommended actions issued for the Scenario A, and using the complementarity, the final recommended care plans is:

- Distress assessment + Mastectomy + Sentinel Lymph Node biopsy + No Axillary Lymph Node Dissection + No Contralateral Prophylactic Mastectomy
- Distress assessment + Lumpectomy + Sentinel Lymph Node biopsy + No Axillary Lymph Node Dissection + Whole Breast Radiation Therapy (WBRT).

Table 1. Comparison of NCCN and ESMO CPGs on Scenario A

Rules	NCCN CPGs	ESMO CPGs
Identical	IF Stage (I OR IIA OR IIB OR T3N1M0) AND No_Clinical_Axillary_Lymph_Node THEN Sentinel_Lymph_Node_Biopsy Recommended WITH Cat. IIA IF Invasive_Breast_Tumor AND Mastectomy_Recommended THEN Surgical_Axillary_Staging Recommended WITH Cat. I	IF Breast_Surgery_Recommended AND No_Clinical_Axillary_Lymph_Node THEN Sentinel_Lymph_Node_Biopsy Recommended WITH Cat. IIA IF Invasive_Breast_Tumor AND Mastectomy_Recommended THEN Sentinel_Lymph_Node_Biopsy Recommended
Complementary (excerpt)	IF Invasive_Breast_Tumor THEN Distress_Assessment Recommended WITH Cat. IIA IF Stage (I OR IIA OR IIB OR IIIA) THEN Mastectomy Recommended WITH Cat. I IF Stage (I OR IIA OR IIB OR IIIA) AND Mastectomy_Recommended AND No_High_Risk_Of_Contralateral_Breast_Cancer THEN Contralateral_Prophylactic_Mastectomy Not_Recommended WITH Cat. IIA	IF Invasive_Breast_Tumor AND (Tumor_Size>3cm OR SBR=3) THEN Sentinel_Lymph_Node_Biopsy Recommended IF Invasive_Breast_Tumor AND Breast_Surgery_Recommended AND No_Clinical_Axillary_Lymph_Node THEN Axillary_Lymph_Node_Dissection Not_Recommended
Conflicting	IF (Stage I OR Stage II) THEN (Lumpectomy AND WBRT) Recommended WITH Cat. I	IF Invasive_Breast_Tumor AND Tumor_Size> 2cm AND No_Wish_For_Conservative_Surgery THEN Mastectomy Recommended

For the Scenario D, we found six concordant rules (3 + 3), 41 complementary rules, 17 from NCCN CPGs, and 24 from ESMO CPGs, and no conflicting rule. Table 2 provides an excerpt of the results.

Table 2. Comparison of NCCN and ESMO CPGs on Scenario D

Rules	NCCN CPGs	ESMO CPGs
Complementary (excerpt)	IF Postmenopausal_Patient AND Adjuvant_Endocrine_Therapy_Recommended THEN 5_Years_Aromatase_Inhibitors Recommended WITH Cat I	IF Positive_Hormonal_Receptors AND Endocrine_Therapy_Recommended THEN Calcium_and_Vitamin D3_Supplements Recommended

4. Discussion

We have compared NCCN and ESMO CPGs on the management of breast cancer. The aim was to assess how much they were in coherence, complementarity, or conflict prior to their implementation in the guideline-based decision support component of the DESIREE system. On a clinical case involving two decisions, we found 16% of concordance, 81% of complementarity, and 3% of conflict.

Globally, CPGs are coherent and using the complementarity of CPGs to enlarge the coverage of decision support seems to benefit the production of enriched recommendations. Complementarity essentially relies on the provision of specific care apart from the breast cancer therapeutic management (e.g. distress assessment, calcium and VIT D3 supplements). The few inter- and intra-CPGs conflicts show the limits of CPGs in particular situations still debated by medical research (e.g. Mastectomy and Lumpectomy are recommended with the same level of evidence by NCCN CPGs). In this case, both recommendations are displayed to MTB physicians to let them make the best decision for the patient. Mixing atomic recommendations issued by NCCN and ESMO CPGs to build a global care plan is another issue. Indeed, the final care plan does not have any level of confidence since there is no algebra to allow such computation. Further work needs to be done to formalize the remaining CPGs and implement the five CPGs in the DESIREE guideline-based decision support.

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