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The Challenge of Radiological Evaluation of T4 Breast Cancer During Neoadjuvant Chemotherapy in a Resource-Limited Country

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Abstract: Locally advanced breast cancer, including Tumor-Node-Metastasis (TNM) stage T4, is the most frequently diagnosed cancer in Burkina Faso. Breast imaging is essential in the initial assessment and evaluation of the response of breast cancers under neoadjuvant chemotherapy (NAC). A therapeutic challenge is posed by the poverty of the population, aiming to rationalise paraclinical explorations, particularly medical imaging. We conducted this study to discuss relevant imaging strategies for the evaluation of tumour response in advanced breast cancer during neoadjuvant chemotherapy in our context of resource-limited countries. It was a cross-sectional descriptive study based on the medical records of patients followed up in the oncology department of the Yalgado Ouédraogo University Hospital. All patients treated for T4 non-metastatic breast cancer and who received at least one course of neoadjuvant chemotherapy were included. The study variables were the socio-demographic characteristics of the patients, the initial evaluation (clinical, radiological, anatomopathological); the mid-term and end-of-treatment evaluation of the ANC (clinical, radiological). T4 patients accounted for 74.28% of non-metastatic cancers diagnosed during the study period. The average age was 46 years. There were 96.15% of non-specific invasive carcinomas. Inflammatory type cancers accounted for 66.67% of cases. Lymph node involvement was present in 89.74%. All patients were classified as stage IIIB according to the UICC (Union for International Cancer Control). Initial, mid-term and end-of-treatment clinical assessments of the tumour were performed in 65.38%, 85.5% and 82.98% of cases respectively. Ultrasound was performed only at the initial stage in 51.28% of cases. CT scans were performed in all these evaluations but did not mention tumour size. The tumour response rate was determined empirically. CT would allow, at the same time as the extension assessment, to perform a loco-regional assessment of the breast tumour in the absence of other dedicated breast imaging.

Keywords: Breast Ultrasound, CT Scan, Tumour Response Rate, Burkina Faso

1. Introduction

Breast cancer is discovered in Burkina Faso at an advanced stage. Several local studies have found high rates of advanced cancer diagnosis: 77%, 82.71% and 58.7% [1–3]. Breast cancers T4 of the TNM (Tumor Node Metastasis) code are among these locally advanced cancers. They include cancers that infiltrate the skin and/or chest wall (T4 a, b, c), as well as inflammatory breast cancer, also known as carcinomatous mastitis. The latter is characterized by diffuse, fleshy skin induration with erysipeloidal edges, usually without underlying palpable tumor [4].

Breast imaging is essential in the initial assessment and evaluation of the response of breast cancers under neoadjuvant chemotherapy (CNA). It uses conventional means such as mammography, ultrasound and magnetic resonance imaging and in recent years, so-called functional imaging (spectro-MRI, positron emission tomography (PET) coupled or not to computed tomography (CT). In our limited-resource countries, patients are often seen with large tumours invading adjacent structures (wall attachment, pain, necrotic skin ulcers) or as carcinomatous mastitis. The neoadjuvant chemotherapy is then the first step of the therapeutic strategy. It aims to significantly reduce the size of the tumour for surgical treatment and to combat micrometastatic disease [5]. Subsequent therapeutic decisions depend on its success. The evaluation of this treatment implies to meet two major challenges: first, the rationalization of the prescription of the paraclinical explorations in front of the indigence of the populations and the absence of universal health insurance; second, the clinical presentations of these tumours, which are often voluminous, painful, ulceronecrotic and inflammatory, limiting the technical feasibility of certain explorations (clinical examination, mammography, ultrasound).

No study at the current state of our knowledge has specifically looked at the contribution of imaging in the evaluation of the tumor response of these advanced T4 cancers in Burkina Faso. We conducted this study to discuss relevant imaging strategies for assessing the tumor response of advanced breast cancers during neoadjuvant chemotherapy in our resource-limited countries.

2. Patients and Methods

It was a transversal study with descriptive aim on the basis of medical records of patients followed in the cancer department of the Yalgado Ouédraogo University Hospital Center for histologically confirmed breast cancer, January 1, 2013 to December 31, 2021. In this study, all follow-up patients for non-metal T4 breast cancer who received at least one neoadjuvant chemotherapy treatment were included. The diagnosis of inflammatory breast cancer (T4d) was made according to the clinical definition proposed by De Vita: heat and erythema over more than 50% of the breast surface, often with cutaneous edema associated with an erysipeloidal and orange peel appearance. The breast is increased in size with or without palpable mass. The symptoms set in quickly, in less than three months" [4]. Neglected breast cancers, which have developed skin signs of inflammation, have not been selected as inflammatory breast cancer. Non-inflammatory T4 breast cancer consists of patients who have a tumor:

1) of any size extended to the chest wall (T4a),
2) of any size extended to the skin (T4b): edema including orange peel, or ulceration of the skin of the breast, permeation nodule located on the skin of the same breast, or inflammatory skin signs affecting less than 50% of the surface of the breast,
3) corresponding to both category T4a and category T4b (T4c).

Not included, patients without parietal and cutaneous invasion, those whose records did not include information related to the assessment of the tumour response, as well as patients who were lost after the first neoadjuvant chemotherapy treatment.

The required information was collected from medical records, surgical records and pathological anatomy. The study variables were related, on the one hand, to patient socio-demographic characteristics, NAC indications, NAC protocols, and tumour response assessment sequences. The variables used to assess the completeness and regularity of the various evaluations were as follows:

1) For the initial assessment, the following information may or may not have been mentioned in the image documents consulted: Tumor size, multifocality for mammography and breast ultrasound; Breast Magnetic Resonance Imaging (MRI) Data, Secondary remote locations objectified to chest abdominal pelvic CT (CT TAP),
2) For mid-term and end of treatment assessment: mammogram or breast ultrasound, breast MRI, chest CT abdominal pelvic, tumor response. The quantitative variables were described by means, their standard deviation, the 1st and 3rd quartile and their extremes. As for the qualitative variables, they have been described by proportions.

Ethical considerations were addressed by anonymizing all data collected from patient files. We presented the study protocol to the Yalgado Ouédraogo University Hospital's management and obtained a written approval. The reference sequence, the routine recommended for the NAC evaluation, was as follows:

1) An initial assessment (clinical, radiological, pathological);
2) A mid-term evaluation of the CNA, after the 3rd or 4th cure, (clinical, radiological);
3) An evaluation at the end of the NAC (clinical and radiological);

The contribution of the various imaging studies available has been analyzed taking into account the advanced breast cancer context.

3. Results

3.1. Patient Characteristics

We collected 78 files that met the inclusion criteria. T4 patients accounted for 74.28% of patients diagnosed with non-metal cancer at the time of the study. The study patient characteristics are summarized in Table 1. The average age of patients was 46.5 years with extremes of 24 and 80 years. Histological analysis showed a predominance of non-specific infiltrative carcinoma in 96.15% of cases (n=75). SBR 2 was the highest in 72.97% of cases (n=54). Inflammatory cancers (T4d) were most common in 66.67% of cases (n=52). Lymph node involvement existed in 89.74% of cases (n=70), with N1 predominance in 61.54% of cases. All patients were classified as Stage IIIB of the UICC classification. Patients receiving at least 6 chemotherapy treatments accounted for 65.38% of the sample (=51).

Table 1. *Characteristics of patients from the records reviewed.*

Variables	Frequency	Percentage
Histological types		
CNOS	75	96.15
Carcinomatous mastitis	2	2.56
ILC	1	1.28
SBR grade (N=78)		
1	13	17.57
2	54	72.97
3	7	9.46
T Category of TNM (N=78)		
T4a	5	6.41
T4b	14	17.95
T4c	7	8.97
T4d	52	66.67
N Category of TNM (N=78)		
N0	8	10.26
N1	48	61.54
N2	18	23.08
N3	2	2.56
AJCC Classification (N=78)		
IIIB	78	100.00

SBR: Scarff-Bloom-Richardson; AJCC: American Joint Committee on Cancer; CNOS: Carcinoma not otherwise specified; ICL: Infiltrating lobular carcinoma;

3.2. Initial Assessment

It covered 78 subjects. Clinical tumor size was measured in 51 patients (65.38% of cases). The average height was 8.2 cm (3-30 cm extremes). There was no significant difference in size between the different categories of the T4 classification (p=0.5788). Ultrasound size was measured in 40 patients (51.28% of cases). The average height was 5.2 cm (extremes of 2.3 to 17.5 cm). There was no significant difference in size between the different categories of T4 to ultrasound (p=0.78). CT TAP was performed in all patients and the tumour size was not described.

Table 2. *Distribution of Patients by Clinical and Imaging Endpoints (N=78).*

Evaluation parameters	Realized		Unrealized	
	Staff	%	Staff	%
Clinical evaluation	78	100	0	0.0
Breast ultrasound	40	51,3	30	48.7
MRI	0	0,0	78	100
CT TAP	78	100	0	0.0

3.3. Mid-term Evaluation

It involved 48 patients, 30 were lost. Clinical evaluation in 42 cases (87.5%). Clinical tumor size at mid-term was assessed in 29 patients. It was measured at 5.06 cm. CT was performed in all cases but did not describe the appearance of the tumor. No patients performed breast ultrasound or breast MRI. A clinical tumor response was performed and found to be partial in 51.06% of cases, stable in 27.66% of cases and progression in 21.28% of cases. There was no complete objective answer.

Table 3. *Distribution of Patients by Parameters of Mid-term Clinical and Radiological Assessment (N=48).*

Clinical parameters	Realized		Unrealized	
	Staff	%	Staff	%
Clinical tumor evaluation	42	87.5	6	12.5
Clinical tumor response	0	0.0	48	100
Breast ultrasound	0	0.0	48	100
MRI	48	100	0	0.0
CT TAP	0	0.0	48	100.0
Tumor response rate	42	87.5	6	12.5

3.4. Final Evaluation

It involved 47 patients. One was carried out following the midterm evaluation. The clinical evaluation was conducted in 39 cases (82.98%). Clinical tumor size was evaluated in 22 patients. At the end of treatment, she averaged 4.3 cm. Chest-abdominal-pelvic CT scans were performed in all patients and there was no description of the tumour. No patients performed breast ultrasound or breast MRI. A clinical tumor response was performed and found to be partial in 63.83% of cases, stable in 8.51% of cases and progression in 27.66% of cases. There was no complete objective answer.

Table 4. *Distribution of Patients by End-of-Course Clinical and Radiological Endpoints (N=47).*

Clinical parameters	Realized		Unrealized	
	Staff	%	Staff	%
Clinical tumor evaluation	39	83	8	17
Clinical tumor response	47	100,0	0	0,0
Breast ultrasound	0	0,0	47	100
MRI	0	0,0	47	100
CT TAP	47	100	0	0,0
Tumor response rate	0	0,0	47	100,0

4. Discussion

Our study showed that breast ultrasound was performed in half of the cases at the initial stage and there was no breast MRI performed. No radiological breast scans were performed at the mid-point or at the end of neoadjuvant chemotherapy.

The extension assessment was performed by chest abdominal pelvic CT at all stages of the NAC assessment, but there was no mention of mammary tumor size.

Assessment of tumor response is clinical and paraclinical.

4.1. Clinical Assessment Tumor Response

The tumour size was poorly performed in 65.38%, 60% and 47% of cases, respectively, at the beginning, mid-course and end of treatment. These low levels can be explained by the appearance of the breast in T4 stages that often appear with ulcerated skin lesions, sometimes necrotic hemorrhagic. Also, the majority of T4 cancers were inflammatory in appearance (66.67%), which can make it difficult to measure a mass in an overall swollen, painful and edematous breast. These T4d cancers were for two cases, true carcinomatous mastitis. The rest correspond to cancers neglected secondarily inflammatory and considered as such [4]. These neglected cancers could increase the rates of some African series: 9.4%, 54%, 37.6%, and 38% [3, 6–8]. These cancers, which are neglected as secondary inflammatory cancers, are due to ignorance, lack of financial resources and the weight of traditional medicine [7]. In western literature, a 1-5% rate of true carcinomatous mastitis is described [9, 10]. These cancers, whether true or neglected inflammatory, are characterized by non-specific signs: thickening of the skin, stromal infiltration, architectural disorganization and a diffuse increase in breast density. In carcinomatous mastitis, there are more specific signs, such as the presence of a mass that is however inconsistent and microcalcifications of malignant appearance. In neglected cancer, the mass is present and is associated with signs of skin and subcutaneous inflammation.

Non-inflammatory T4 cancers are characterized by parietal and or cutaneous involvement, regardless of the size of the mass. For non-mestatic T4 cancers, the primary objective of the CNA is to improve loco-regional control and patient survival [5]. Lymph node involvement was noted in 89.74% of cases (n=70), with N1 predominance in 61.54% of cases. All patients were classified as Stage IIIB of the UICC classification.

Neoadjuvant chemotherapy was complete in approximately 2/3 of cases (65.38%). In-course evaluation of chemotherapy was clinical and para-clinical. It analyzes the appropriateness of continuing a treatment that is not only costly, but also has side effects. It also predicts the histological response, an important survival factor [11].

Clinical evaluation is important but can be faulted, especially in case of breast edema or ulceration limiting palpation of the underlying mass. The regression of inflammatory phenomena, present in inflammatory cancers can also underestimate the tumor lesion.

4.2. Paraclinical Assessment Tumor Response

The baseline for assessing tumor response is histology [12]. But before surgery, medical imaging allows to assess the tumor response. This evaluation must be based on specific and objective criteria. RECIST criteria allow reliable and reproducible measurements [13]. According to the 2009 version, for target lesions:

1) the complete response: disappearance of all target lesions, confirmed by a new examination performed at 4 weeks;
2) partial response: at least a 30% reduction in the sum of the largest diameters of each target lesion, taking as a reference the initial sum of the largest diameters, confirmed by a new examination carried out at 4 weeks;
3) tumor progression: increase of at least 20% of the sum of the largest diameters of each target lesion, taking as reference the smallest sum of the largest diameters reported since the start of treatment, or the appearance of one or more new lesions;
4) tumor stability: tumor decrease insufficient to define a partial response and/or tumor increase less than necessary to define tumor progression, taking as reference the smallest sum of the largest diameters since the start of treatment.

For non-cible lesions:

1) The complete answer: disappearance of all other lesions and normalization of tumor markers;
2) Incomplete response/tumor stability: persistence of one or more other lesions and/or persistence of tumor marker value above normal values;
3) Tumor progression: appearance of one or more new lesions and/or frank progression of the other existing lesions In no case was the tumor response assessed by these criteria.

These RECIST criteria can be applied to all imaging media. To explore the breast tumor and evaluate its evolution under neoadjuvant chemotherapy, there are several imaging methods.

4.3. Mammography

It's the most common technique used to detect breast cancer at the subclinical stage. It can detect four types of lesions suggestive of breast cancer: mass, architectural distortions, focal asymmetry of density and microcalcifications. Mammography is more sensitive for detecting these abnormalities in low breast density [14]. The assessment of tumor size depends on the appearance of the lesion. The more irregular or spiculated the contours of the lesion, the more imprecise the measurement. In the case of carcinomatous mastitis, the most common lesions are increased density and breast trabecculation, as well as thickening of the skin [15]. These aspects, which predominate in our study, are visible on the initial evaluation, but are more difficult to evaluate afterwards. An underlying mass is inconstant, which can make the clinical examination non-objective. Technically, when the tumour is large or in case of carcinomatous mastitis, it is difficult to perform adequate breast compression [15]. The same applies to situations where there is a cutaneous ulceration. These situations, which are common in T4 classes, constitute one of the limits to the achievement of this modality whose cost is 20,000 to 35,000 XOF. The difficulties of realization of the mammography as well as its interpretation in

these cases, require the realization of a complementary technique which is the breast ultrasound.

4.4. Breast Ultrasound

Unlike mammograms, it is more effective when the breasts are dense, offering a good contrast between the normal glandular tissue and the tumor. This modality is relatively accessible in our context and its amount is on average 10,000 XOF. The assessment of tumor size is easier the more the lesion is well limited. It has the advantage to explore in addition to the tumor in the three planes of space, to measure the thickness of the cutaneous planes especially in inflammatory cancers and to look for suspect axillary nodes. In inflammatory cancers, skin thickening is visible in 96%, and may be the only sign of this condition, making ultrasound an excellent means of surveillance [16]. However, the increase in the overall echogenicity of the mammary gland in relation to the edema of the subcutaneous planes, may limit the visualization of an underlying mass or an abnormality of glandular echogenicity. In the case of architectural distortions or tumors with irregular contours, tumor measurement can be difficult. The presence of a peripheral halo may overestimate or underestimate the actual size of the lesion depending on its integration or not in the measurement.

Ultrasound is also limited in case of cutaneous ulcers, or bulky tumors that do not allow adequate tumor measurement. These aspects may explain the low rate of ultrasound during the initial assessment and at mid-term and end-of-treatment assessments. Despite these limitations, its superiority over mammography is clear to assess tumor size. It detects more additional lesions than the clinic and mammography and is interesting for looking for multifocal lesions [15]. These limits are lifted by the realization of magnetic resonance imaging.

4.5. Magnetic Resonance Imaging

It's the baseline for initial assessment and follow-up of breast tumours under neoadjuvant chemotherapy, especially when conservative surgery is involved. It has a sensitivity of about 93 to 100%. It is effective in the analysis of inflammatory cancers by analyzing tumor vascularization. It is free from the tumor volume and from the extension to the cutaneous planes and to the wall. It allows depending on the initial appearance of the tumor to predict the tumor response. Circumscribed forms tend to respond better to treatment than fragmented forms [17]. However, MRI is not functional in the public structures of our country and the cost of realization is 150,000 XOF, representing five times the guaranteed minimum wage in Burkina Faso. Its availability and reduced accessibility is its real limitation in our context and may explain the almost absence of this examination in our study (< 1%).

4.6. CT Scan

However, during the initial assessment, CT scans were performed in all patients. It allows to adjust the line to hold in case of secondary lesions. CT is not specifically indicated in the local breast cancer scan. But, by exploring the thoracic stage, it allows to visualize at the same time the mammary glands. Several authors recommended that radiologists examine the mammary glands during chest CT scans because the frequency of breast abnormalities is high [18, 19]. Seventeen to 50% of breast incidentalomas seen at CT were cancers [20].

However, tumour and lymph node size can be assessed at CT, especially for locally advanced cancers [21]. In the case of inflammatory and non-inflammatory cancers, this modality could be a good complement to the clinical examination to assess the lesions, in the absence of another dedicated imaging performed. It is not limited by the presence of ulcerations of the cutaneous planes. It would make it possible to measure the thickness of the cutaneous planes, to appreciate the importance of edema and subcutaneous infiltration and to measure a possible tumor, especially in inflammatory cancers, present mainly in our sample. In the mediastinal window, the breast tumor is visible and can be measured in all three planes of space, regardless of its size. The tumor, initially targeted could be monitored during CT scans at mid-term and end of NAC treatment. Similarly, by this technique, the contralateral breast is also explored. The same is true for the lymph nodes that were mostly affected in our series. CT scan would analyze their number, appearance and size during this exploration.

However, in our study, no mammary tumor size was performed at CT. Radiologists probably did not see the value of this and would focus more on the search for a regional and remote metastatic extension. It would also clarify the number, appearance and size of regional loco nodes.

It is true that most of the studies that have proposed CT to evaluate the mammary tumor response are old, functional imaging including perfusion, spectroIRM and PET/CT sequences quickly outperformed it. Indeed, in addition to the morphological appearance of the tumor, these functional imageries can predict the tumor response to the CNA. This technique can be faulted in case of abundant glandular tissue, masking the tumor lesion. Despite these limitations, it would provide additional arguments to support the clinical examination.

Several authors have emphasized the interest of combining breast ultrasound, breast MRI with clinical examination and mammography for the search for multifocality and multicentricity during the initial assessment. However, to assess tumor response, MRI is superior to mammography combined with clinical examination. In our context, where the costs of para-clinical examinations and cancer treatment are borne by patients and their families, not all prescribed examinations can often be carried out in a timely manner. Due to the advanced stage during the management of these patients, mastectomy is most often performed and assessment of tumor response is clinical.

Financial reasons are certainly important. Knowing that the majority of the patients were housewives, and knowing the socio-economic context in which we live, The addition of additional breast scans could be an additional challenge for patients whose treatment and para-clinical examinations are often managed by those around them. The question arises for

the oncologist to streamline the prescription of imaging means in these situations of precariousness, while ensuring an efficient evaluation of the tumor.

5. Conclusion

T4 cancers are a special feature of breast cancers, common in our context. Tumour evaluation in neoadjuvant chemotherapy involves several different means of utility, relevance and feasibility, such as mammography, breast ultrasound, magnetic resonance imaging and functional imaging.

In the context of countries with limited resources, the most cost-effective means are computed tomography, which makes it possible not only to carry out an extension assessment, but also a regional loco evaluation of breast disease.

Other means not yet available in our context could be of additional use in breast cancer assessment. But above all, it is imperative and indispensable to put in place measures for the early diagnosis of breast cancer.

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