Management of Breast Cancer Locoregional Recurrence

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Rezumat

Managementul cancerului mamar recidivat locoregional

Recidiva în cancerul mamar reprezintă o provocare pentru clinician din cauza tratamentului nestandardizat și necesită de obicei o abordare multidisciplinară. Aceasta este cheia pentru un control bun al bolii pe termen lung și pentru un tratament cu intenție curativă. Recidiva locală în cancerul mamar poate apărea după tratamentul chirurgical conservator sau după mastectomie iar recidiva regională implică limfonodulii ipsilaterali axilari, mamari interni sau supraclaviculari. Prognosticul recidivei locale după tratamentul chirurgical conservator pare să fie mai bun decât după mastectomie în termenii apariției metastazelor la distanță și a supraviețuirii globale. De asemenea, prognosticul recidivei axilare este mai bun decât cel al recidivei supraclaviculare sau mamare interne. Recidiva locoregională în cancerul mamar reprezintă mai degrabă un marker al apariției metastazelor decât un factor determinant al acestora. Opțiunile terapeutice pentru recidiva loco-regională în cancerul de sân impun decizii multidisciplinare și din acest motiv este foarte importantă comisia oncologică multidisciplinară. Fiecare pacient trebuie să primească cel mai bun tratament oncologic personalizat.

Cuvinte cheie: recidiva locoregională, tratament multimodal, marker al apariției metastazelor

Abstract

Breast cancer recurrence represents a challenge for clinicians because the management is not standardized and usually requires

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a multidisciplinary approach. This is the key for a good long term disease control and for a management with curative intent. The local recurrence in breast cancer appears after breast conserving treatment (BCT) or after mastectomy, and the regional recurrence involves the ipsilateral axillary, internal mammary or supraclavicular lymph nodes. Local recurrence prognosis after BCT seems to be better than after mastectomy regarding distant metastases occurrence and overall survival. Prognosis of axillary recurrence is better than prognosis of supraclavicular and internal mammary recurrence. Locoregional recurrence in breast cancer represents rather a marker for the appearance of distant metastases than a determinant factor for them. Management options for locoregional recurrence of cancer require multidisciplinary input decision making and for this reason the multidisciplinary tumor-board (MTD) is very important. Each patient should receive the best individualized oncologic treatment.

Key words: locoregional recurrence, multimodality treatment, marker of distant metastases

Introduction

The breast cancer recurrence is a very serious event for patient and clinician also and represents a challenge for at least two reasons: the recurrence seems to be a marker of distant metastases and its management rarely consists of just one specialty procedure, but needs a multimodality treatment. Multidisciplinary treatment is the key for a good long term disease control and for curative intent management.

Some potential theories that try to explain the development of recurrence take into account the following factors (1):

- Incomplete excision of primary tumor;
- Unrecognized multifocal or multicentric disease;
- Implantation of tumor cells at time of surgery;
- Entrapment of cells within obstructive lymphatic;
- Local implantation of systemically circulating cancer cells.

Breast Local Recurrence

Breast recurrence represents the reappearance of cancer in the remaining breast after breast conserving treatment (BCT) or in the soft tissues of the anterior chest wall after mastectomy in a patient with no evidence of disease after primary treatment. Some authors consider that tumor recurrence in less than one

year after surgery has a worse prognosis and represents rather a continuation of the disease progression than an actual relapse. For this reason this type of relapse is called continuation of evolution and it is not addressed in this paper.

Local Recurrence after BCT

The incidence rate of local recurrence after BCT ranges from 10% to 22% at 10 years (2,3,4) and its median time of appearance is 3-4 years (5-7 years after use of adjuvant systemic therapy) (5,6).

In 5-15% of cases, local recurrence is associated with concomitant distant metastasis and in other 5-15 % of cases with regional disease. These 10-30% of patients with simultaneous regional or distant relapse have a worse prognosis than patients with isolated local recurrence (5,6,7).

The appearance of a breast mass after BCT could represent a true local recurrence or a second primary tumor (a new breast cancer). Usually the differential diagnosis is very difficult, sometimes quite impossible, but the prognostic and therapeutic significance of this difference (relapse or new primary) is not clear yet.

The prognosis of local recurrence after BCT seems to be better then after mastectomy, with a lower rate of simultaneous regional recurrence or distant metastasis and a longer survival. However, the relation between local recurrence after BCT and survival remains

controversial because recurrence seems to be rather an independent risk marker predictive for distant metastases than a determinant factor (cause) for metastasis occurrence (8,9).

Two factors are considered principal determinants of local recurrence after BCT (10):

- margin status;
- the presence or absence of an extensive intraductal component (EIC).

BCT should aim to achieve microscopically negative margins (no tumor cells at the resection margins), although there is no direct relationship between margin width and rates of local recurrence. EIC seems to be highly predictive for local recurrence after BCT and is probably predictive for positive margins also.

Other contributing factors for relapse after BCT are (11,12,13,14):

- No radiotherapy;
- Age under 35;
- Tumor size greater than 2 cm in maximum diameter;
- The presence of lymph vascular invasion;
- High tumor grade;
- The presence of lobular carcinoma;
- Small volumes of excised breast tissue;
- No chemotherapy and/or hormonal therapy.

The standard approach for local recurrence management after BCT is mastectomy with or without immediate reconstruction of the breast. Reconstruction after mastectomy for local recurrence after BCT seems to be controversial because there are some unanswered questions:

- Which is the best: immediate or delayed reconstruction?
- Does reconstruction lead to a higher risk for a second local recurrence or not?
- Reconstruction with implants or autologous tissues? Which one provides safer and better cosmetic results?

In case of inflammatory local recurrence, systemic therapy is mandatory and only after a clinical response to therapy (disappearance of inflammatory changes) mastectomy seems to be feasible.

The patients who were treated only by surgery (no radiotherapy) can undergo either mastectomy or reexcision followed by radiation

but, in this latter situation, there is also a debate: after breast reexcision and radiation would be possible an acceptable cosmetic outcome?

The most complicated situation is for the patients with local recurrence after breast conservative surgery and radiation that are not willing to undergo mastectomy. In this case breast reexcision is possible, followed or not by reirradiation of the remaining breast additional radiation.

The approach is still debatable for many reasons (15,16):

- a possible high rate of second local recurrence;
- an unfavorable cosmetic outcome;
- the uncertainty of technical feasibility of breast reirradiation (brachytherapy or external beam).

The local recurrence after BCT may be associated with regional recurrence (especially axillary lymph nodes). The management of the axilla depends on the following factors (1):

- Previous axillary surgery: none or sentinel lymph node (SLN) biopsy or axillary lymph node dissection (ALN);
- The initial stage of disease;
- The presence of distant metastases;
- The adjuvant therapies.

Patients with previous ALND and no clinical or imagistic evidence of regional disease need only simple mastectomy (no axillary restaging). For patients with previous negative SLN, an option could be repeating SLN biopsy. The rate of success for the new SLN procedure ranges from 63% to 100% in different published studies (17,18,19). There are few questions about the possibility of axillary restaging (20,21):

- Is rate of axillary recurrence higher after repeated SLN biopsy?
- Is procedure sensitivity sufficiently high?
- What about the likelihood of aberrant drainage pattern? Is it higher than in the first procedure?
- Is lymphoscintigraphy still possible after radiotherapy?

For simultaneous distant metastases, patients with local breast recurrence need

systemic therapy and the goal of treatment in this situation is palliation (no intent to cure).

Surgery for local relapse in a patient with concomitant distant disease is reserved only for those cases with enlarged, ulcerated, over-infected or bleeding recurrences aiming a better local control and to increase the quality of life.

Another situation is surgery for isolated symptomatic metastases for patients with a good health status. The intent of this type of surgery is also palliation (no evidences for improving survival).

Systemic therapy for patients with no evidence of distant metastases remains controversial, but should be considered, and the risk-benefit ratio must be discussed with patients. For triple negative tumors (ER negative, PR negative and HER 2 negative) chemotherapy is mandatory.

Subsequent recurrence rate after mastectomy performed for relapses after BCT ranges between 2% and 32%, which is significantly lower comparative with recurrence rate after simply reexcision of relapse after BCT, that vary from 19% to 50% (6,22,23).

The 5 year local control was better for recurrences occurring more than 5 years after initial treatment (92%) than within the first 5 years (49%), while the 5 years overall survival (OS) ranged from 45% to 80% and the 10 years ranged from 40% to 65% (24,25).

There are some factors associated with a worse outcome for patients with local recurrence after BCT (1):

- Inflammatory type of recurrence;
- Advanced stage of the primary tumor;
- Short interval between primary treatment and recurrence (short disease free interval);
- Large recurrent tumors with skin or muscle involvement;
- Multicentric tumor recurrence;
- Triple negative tumors.

Local Recurrence after Mastectomy

Local recurrence rates after mastectomy ranges from 5% to 15% at 10 years after treatment with a median time of appearance of just 2-3

years (even later, in case of systemic therapy administration) (1,5,26). Approximately 80% to 90% of local recurrences appear within 5 years after mastectomy and nearly all in the first 10 years. (27,28) Association with regional recurrence occurs in 30% of cases (29,30). About 50% of patients with local recurrence after mastectomy will develop earlier or later distant metastases (28,31).

For this type of local recurrence, the amount of breast tissue left behind during mastectomy is the determinant factor. By comparison with local recurrence after BCT, the recurrence after mastectomy is more likely to be associated with a higher risk of distant metastases and a more unfavorable prognosis (shorter overall survival). Thus local relapse after mastectomy seems to be rather an independent predictor (risk marker) for distant metastases development than a determinant factor of their occurrence (10).

For resectable recurrence all gross disease must be excised and sometimes a type of tissue transfer procedure is necessary for wound closure: skin grafts or myocutaneous flaps. For patients no previous irradiated this type of technique is recommended for a better local control.

For patients who have had reconstruction without radiation, the removal of implants or flaps remains controversial because although future irradiation seems to be feasible it implies an increased risk of implants capsular contraction or even autologous flaps contraction.

The majority of recurrences after mastectomy occur in patients that had both mastectomy and radiotherapy, and in this case, surgery remains standard of care because reirradiation induces a significant risk of tissue damage and is technically difficult to perform. (32,33)

In the presence of concomitant distant metastases, patients are subjected to systemic therapy (chemotherapy and hormonal therapy). Conversely in the absence of distant metastases the use of systemic therapy remains debatable because of the small documented benefit on OS rate.

In literature there are described few other alternatives for treating local recurrence after

mastectomy and radiation, such as (34,35, 36,37):

- hyperthermia (the temperatures ranges from 40 to 45 C);
- photodynamic therapy (FDT);
- intraarterial regional chemotherapy;
- electrochemotherapy.

These techniques are new, controversial and are not yet a real alternative to surgery and radiotherapy.

For patients with resectable isolated local recurrence after mastectomy (no regional or distant metastasis) OS rate ranges from 35% to 80% at 5 years and 25% to 60% at 10 years (25). The 5 and 10 years actuarial rates of OS are 50% and 26% (38).

Some factors seem to influence survival after local recurrence treatment in patients with mastectomy (29,38,39):

- short free relapse interval;
- advanced stage of disease;
- axillary lymph nodes invasion;
- high tumor grade;
- age under 35 years;
- triple negative tumors;
- no prior adjuvant treatments.

Regional Recurrence in Breast Cancer

Regional recurrence in breast cancer represents the reappearance of cancer to the regional lymphatic basins in a patient with no evidence of disease after primary treatment.

Incidence rate for regional recurrence in breast cancer, isolated or associated with local recurrence, ranges from 1% to 10% (40,41). It seems that regional relapse has increased with current use of SLN biopsy.

If there are no concomitant distant metastases, the management has curative intent. For patients who had a previous SLN biopsy, only a complete ALND is recommended. For patients who had a previous ALND, excision of the relapse is mandatory. Surgery in case of axillary recurrence can be very difficult because of the possible invasion of different axillary structures like muscles, vessels or nerves.

After complete resection of the axillary

recurrence in a patient with no previous axillary radiation, radiotherapy is highly recommended because the risk of a secondary axillary relapse is high. In patients with mastectomy and no previous radiation, adding radiotherapy provides a better local control.

A real challenge is represented by patients who have had prior radiation on the axilla and incomplete excision of recurrence because repeating axillary irradiation is not usually technically feasible (1). For unresectable axillary relapses, systemic therapy and radiation are recommended only for patients without history of radiation; for patients who had already have radiotherapy, a possible solution could be reirradiation.

The prognosis of patients with axillary recurrence is better than for those with supraclavicular or internal mammary relapses (lower risk for distant metastasis and higher overall survival) (42). The management of supraclavicular and internal mammary recurrences involves systemic therapy, irradiation and sometimes surgery for diagnostic or curative goal, but the outcome is poor despite the treatments.

Conclusions

Newer treatments options require newer standard of care for primary tumor and recurrence also. Management options for breast cancer locoregional recurrence requires multidisciplinary input in decision making.

The multidisciplinary tumor-board (MTB) became very important, encompassing members from different disciplines: surgery, plastic surgery, medical oncology, radiation oncology, imaging, pathology and general practice. The communication between its members is vital for implementation of an individualized management plan for each patient with breast locoregional relapse because every patient should receive the best possible individualized care.

It seems that large multicentric randomized trials will be necessary in the future to define more precisely the factors influencing the occurrence and further evolution of breast cancer locoregional recurrence and also for better understanding the recurrence prognostic

significance (marker or determinant factor for distant metastases), in order to establish an initial therapeutic strategy that significantly reduces the risk of relapse.

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