

Optimization of adjuvant radiotherapy in the context of de-escalated surgical management for early breast cancer

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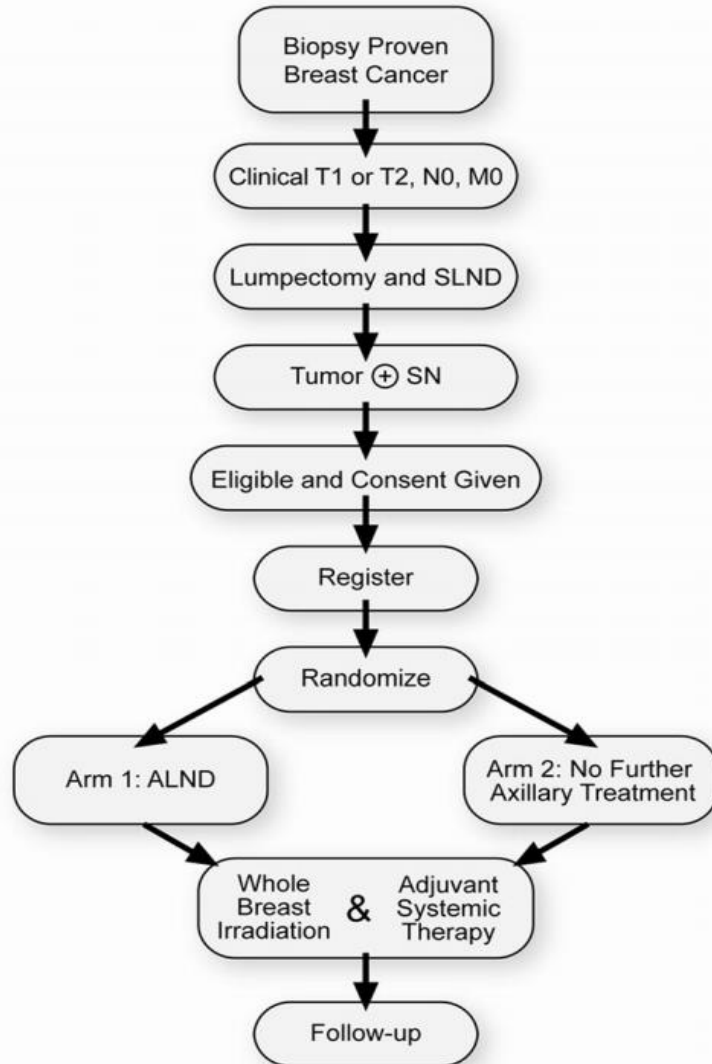


- ACOSOG Z11
- IBCSG 23-01
- AMAROS TRIAL
- OTOASAR TRIAL

Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases

The American College of Surgeons Oncology Group Z0011 Randomized Trial

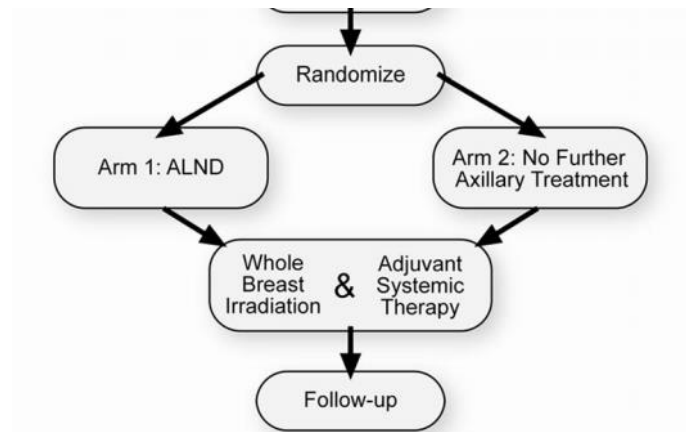
Z0011 Study Design Schema



- **axillary lymph node dissection vs. no dissection (type of surgery)**
- **446 vs 445pts**
- Inclusion Criteria:
 - T1-2 tm,
 - No Axillary palpable lymph node
 - At least 3SLN should be removed and
 - Max 2 or less SLN (+)
- Exclusion criteria:
 - If 3 or more SLN were positive, They went to ALND
 - Mastectomized pts
 - Multicentric disease
 - Matted nodes or extranodal disease
 - Prepectoral implants

The American College of Surgeons Oncology Group Z0011 Randomized Trial

- They are early stages!!
- This study is not a real comparison trial between Surgery and Radiotherapy
- Because



- Where is the Radiotherapy in this trial?
- Whole breast tangential RT in **all** pts. There is no third RT Portal.
- It is accepted that Axillary level I-II were irradiated from lateral tangential field

The American College of Surgeons Oncology Group Z0011 Randomized Trial

- The main end-point was overall survival. All patients had to have a breast conservative procedure and adjuvant irradiation.
- At 6.3 years median follow up: (2010)
- Overall survival: no difference SLND vs ALND
- Criticism of this study
 - Most of the pts ER(+)
 - Follow-up Time was short
- At 9.3 years median follow-up: Update-2017
- Overall survival: SLND vs ALND: 86.3% vs 83.6%
- 10 year DFS: SLND vs ALND: 80.2% vs 78.2%
- 10 year regional recurrence : no difference

Key Points

Question Is there any diminution in 10-year overall survival for women with cT1-2N0 breast cancer and metastases to 1 or 2 sentinel lymph nodes undergoing breast-conserving surgery, whole-breast irradiation, and adjuvant systemic therapy treated with sentinel node dissection alone compared with that of patients treated with axillary dissection?

Findings In this randomized clinical trial including 856 women, after median follow-up of 9.3 years, overall survival for patients treated with sentinel lymph node dissection alone was not inferior to those treated with completion axillary lymph node dissection (86.3% vs 83.6%, respectively; noninferiority hazard ratio margin of 1.3).

Meaning These findings do not support the use of axillary lymph node dissection when metastases are found with sentinel lymph node sampling in women with cT1-2M0 breast cancer.

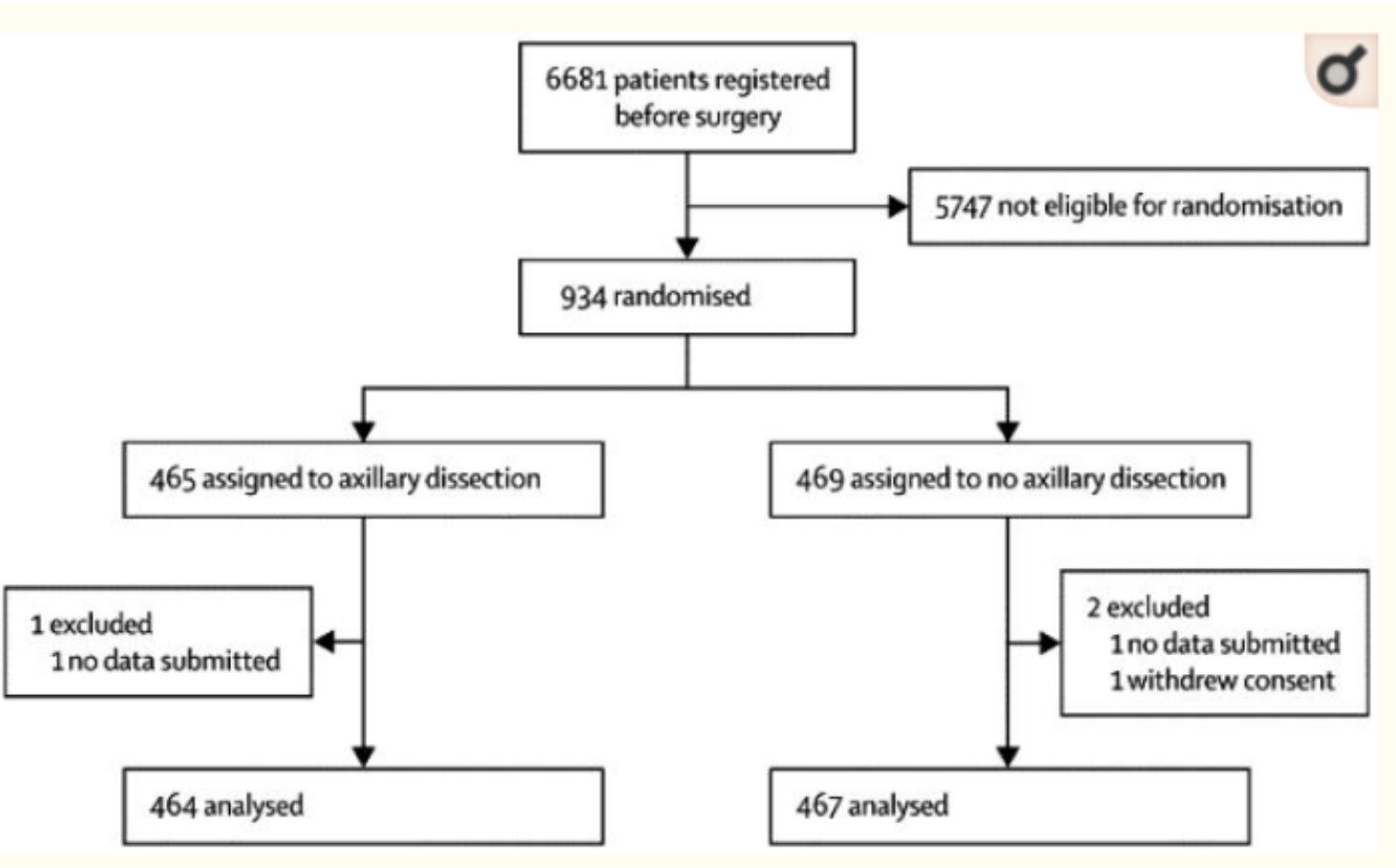
The American College of Surgeons Oncology Group Z0011 Randomized Trial

- The 10-year follow-up data of the ACOSOG Z0011 trial confirmed that when the sentinel nodes had little macrometastatic involvement, further surgical treatment of the axilla was not necessary provided that patients **received whole-breast radiotherapy and systemic treatment.**
- At approximately same time period another study came from Italy
- The IBCSG 23-01 trial compared again axillary lymph node dissection vs. no dissection, but only in case of **micrometastases**,
- Disease-free survival was the main end-point.
- Almost all women in the Z0011 trial received systemic therapy, and 301 (35%) of 856 randomly assigned patients had **micrometastatic** sentinel node involvement and thus were similar to patients enrolled in the IBCSG 23-01 trial.

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases

IBCSG 23-01 randomised non inferiority trial

- clinically non-palpable axillary lymph node(s) and a primary tumour of 5 cm or less and who, after sentinel-node biopsy, had one or more **micrometastatic (≤ 2 mm)** sentinel lymph nodes with no extracapsular extension



There is heterogeneity in radiotherapy. Heterogeneity for no axillary dissection group. Some of them of pts had partial radiotherapy (IORT), some of them had whole breast radiotherapy and some of them had no radiotherapy

IBCSG 23-01 randomised non inferiority trial

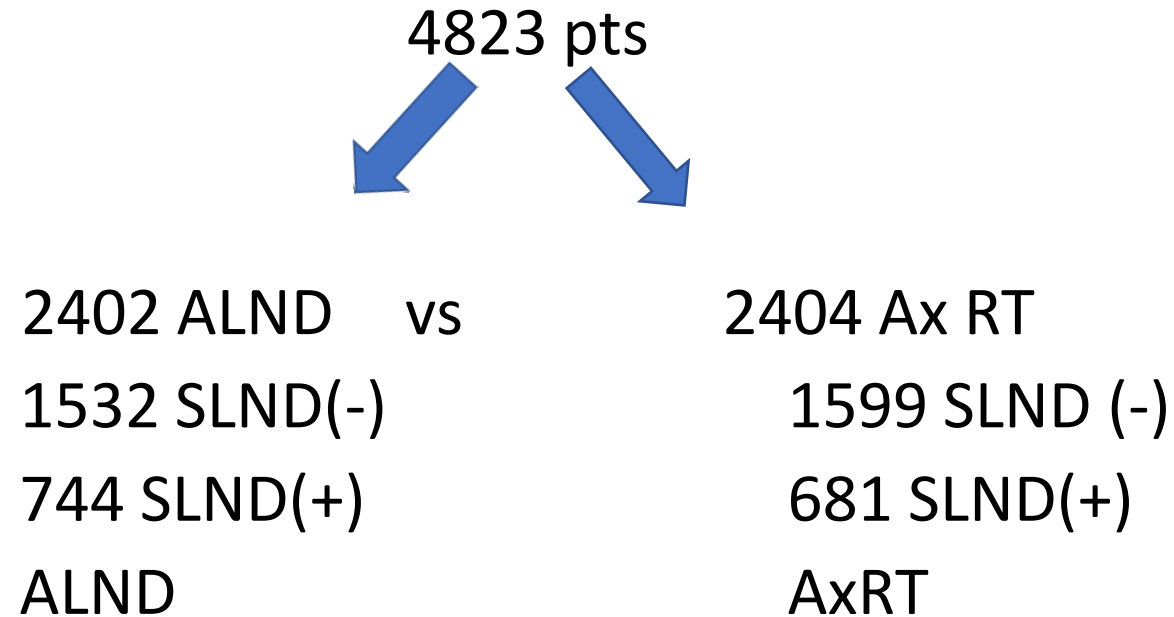
Median follow-up: 9.7 years

	No axillary diss	Axillary diss	
• DFS at 10 years	76.8%	74.9%	p=0.24
• Local recurrences	16%	16%	
• Regional failures	3%	3%	
• Ipsilateral axillary failures	2%	1%	
• Distant metastases	9%	10%	
• Contralateral breast	2%	3%	
• Long-term surgical complications			
lymphoedema	4%	13	
sensory neuropathy	13%	19%	
motor neuropathy	3%	9%	

IBCSG 23-01 randomised non inferiority trial

- Added value of this study The 10-year results of the IBCSG 23–01 trial provide important, additional level-1 evidence that omitting axillary dissection **when the sentinel nodes contain only micrometastases is safe**, supporting the avoidance of potentially serious and chronic sequelae of this surgery in women with early breast cancer

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial



The main hypothesis was to obtain less than 4% axillary recurrence rate in the postoperative nodal irradiation arm

This trial planned was non inferiority trial but is unpowered due to low number of axillary recurrences. (0.43% vs 1.19%)

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer ([EORTC 10981-22023 AMAROS](#)): a randomised, multicentre, open-label, phase 3 non-inferiority trial

- T1-2 tm unifocal, invasive breast cancer, no palpable lymph node and the tumor diameter should be 3cm or less
- Axillary treatment had to start within 12 weeks after the SLNB.
- Consequently systemic therapy was used if there is an indication
- ALND consisted of at least level I-II and removed at least ten nodes
- AxRT included all three levels of axilla and SCF .Dose schema: 2*25fr. Total dose: 50Gy
- Adjuvant AxRT after ALND was allowed if there were 4 or more positive nodes

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (**EORTC 10981-22023 AMAROS**): a randomised, multicentre, open-label, phase 3 non-inferiority trial

	ALND	AxRT
Axillary recurrence :	4 pts (0.43%)	7pts (1.19%)
DFS:	86.9%	82.7%
Overall survival	93.3%	92.5% no difference

Median follow-up: 6.1 year

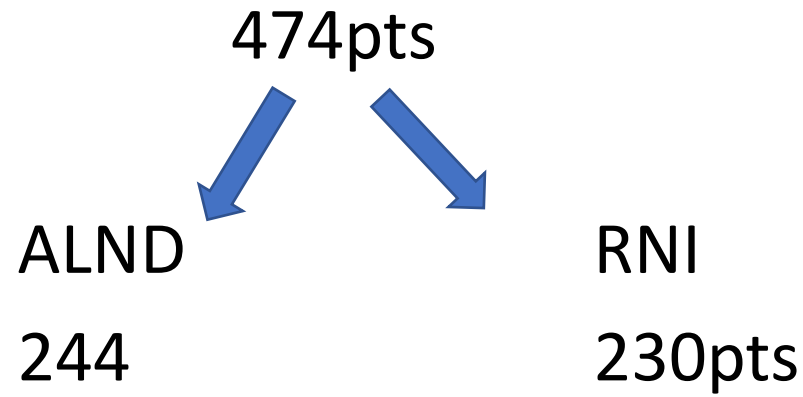
- **Lymphoedema** in the ipsilateral arm was noted **significantly more** often after **axillary lymph node dissection** than after axillary radiotherapy at 1 year, 3 years, and 5 years. (At 5 years %23 for ALND vs 11% for SLND)
- **No significant differences in range of shoulder motion were recorded between the two treatment groups** in all four excursions. A numerical but non-significant increase in restriction of arm mobility in the axillary radiotherapy group compared with the axillary lymph node dissection group at 1-year of follow-up disappeared in the following years.

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (**EORTC 10981-22023 AMAROS**): a randomised, multicentre, open-label, phase 3 non-inferiority trial

If further axillary treatment is needed in clinically node-negative, sentinel-node-positive patients, **axillary radiotherapy could be chosen** instead of axillary lymph node dissection because it provides comparable axillary control and less morbidity.

Eight-year follow-up result of the **OTOASOR trial**: The Optimal Treatment Of the Axilla of Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial

- cNo cT \leq 3cm pts randomized, Hungarian National Institute of Oncology



Primary endpoint was axillary recurrences

Secondary endpoint was OS and DFS

Eight-year follow-up result of the **OTOASOR trial**: The **O**ptimal **T**reatment **O**f the **A**xilla of **S**urgery **O**r **R**adiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial

- Median follow up 97 months

	ALND	RNI	
• Axillary recurrences	2%	1.7%	
• OS at 8 years	77.9%	84.8%	p: .06
• DFS	72.1%	77.4%	p: .51
• Complication rate	15.3%	4.7%	at 1 year
• (Life Quality analysis)			
• The mean number of removed sentinel lymph node was 1.83 on ALND arm 1.95 on RNI arm			
• The mean number of removed in ALND arm 14.31.			
• The mean number of removed positive nodes was 2.77 in ALND arm vs 1.17 in RNI arm			
• RT Technique: all levels of axilla and SCF were irradiated with 2Gy*25fr schema			
• If there is 4 or more positive nodes after ALND or 1-3(+) nodes but high risk characteristics (LVI,premenaposal status or grade III) adjuvant irradiation was applied			

Eight-year follow-up result of the **OTOASOR trial**: The **O**ptimal **T**reatment **O**f the **A**xilla of **S**urgery **O**r **R**adiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single center, phase III, non-inferiority trial

- The long-term results of the OTOASOR trial confirm the concept that in patients with **limited sentinel node metastasis** axillary radiotherapy could be an alternative treatment for selected patients. The trial shows equivalent survival and locoregional control for patients with axillary lymph node metastasis by SLNB with reduced morbidity if treated with RNI instead of cALND

Results of these trials

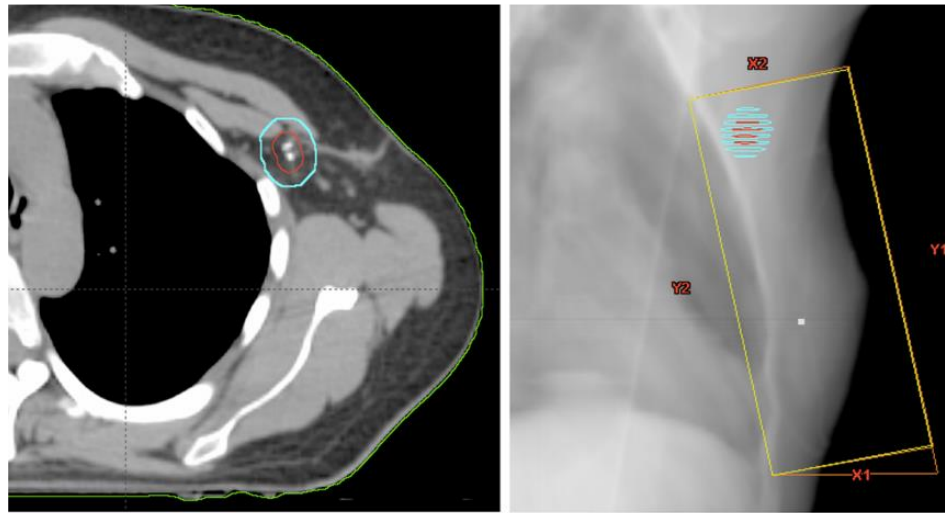
- In view of these trials, axillary lymph node dissection is not required if there was less than three positive sentinel lymph nodes and no extracapsular extension
- These trials have included a small number of patients with isolated tumour cells; but for this group, the risk of residual disease and axillary recurrence is very low and it could be assimilated to a pN0.
- At this moment, surgery trials are now looking at the omission of sentinel lymph node biopsy during breast-conserving surgery, in case of cN0 after a negative axillary ultrasound

MIRROR Analysis

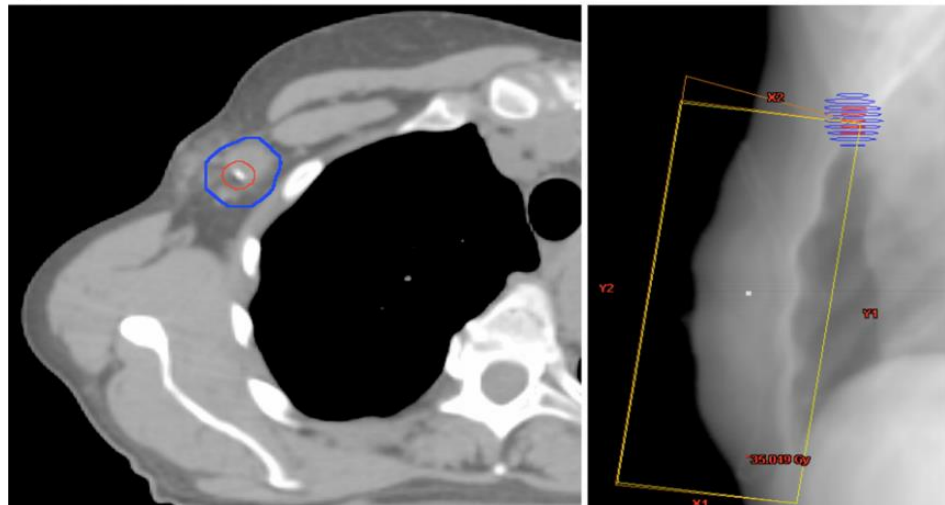
Ann Surg 2012;255:116–21.

- In the MIRROR analysis a large cohort study,
 - the rate of axillary recurrence without axillary treatment (surgery or radiotherapy):
 - 2% for isolated tumour cells
 - 5.6% for micrometastases
 - the rate of axillary recurrence with axillary treatment:
 - 0.9% for axillary surgery
 - 1% for axillary radiotherapy
- ➔ The difference was highly significant for pN0mic between treated and untreated groups.
- However, in the IBSCG trial, 29% of the patients had no postoperative radiotherapy without any difference in locoregional control
 - ➔ Therefore, the usefulness of postoperative radiotherapy in case of micrometastases may be discussed further.

Which type of Radiotherapy should be done



(b)



- Because of the tangential fields including a large part of the axilla, this area must be considered as a target volume in case of micro or macro-metastases. The usefulness of high tangential fields is a matter of discussion.
- It has been estimated that with standard tangential fields, levels I, II and III of the axilla were covered on **66%, 44% and 31%**, respectively, whereas **86%, 71% and 73%** were covered with high tangential fields
- In patients with metastases in SLN without complementary ALND, TgF are expected to cure potential residual disease in the axilla

SURGICAL AXILLARY STAGING - T0,N1,M0; T1-3,N0-1,M0 DISEASE

