Does the Result of Completion Axillary Lymph Node Dissection Influence the Recommendation for Adjuvant Treatment in Sentinel Lymph Node Positive Patients?

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Aims: The Hungarian National Institute of Oncology has just closed a single-centre randomized clinical study. The OTOASOR (Optimal Treatment of the Axilla – Surgery or Radiotherapy) trial compares completion axillary lymph node dissection (ALND) to regional nodal irradiation (RNI) in patients with sentinel lymph node-positive (SLN+) primary invasive breast cancer. In the investigational treatment arm patients received 50 Gy RNI instead of completion ALND. In these patients we had information only about the SLN status, but the further axillary nodal involvement remained unknown. The aim of this study was to investigate whether the result of completion ALND influenced the recommendation for adjuvant treatment in SLN+ breast cancer patients.

Patients and methods: Patients with SLN+ primary breast cancer were randomized for completion ALND (arm A-standard treatment) or RNI (arm B-investigational treatment). Adjuvant systemic treatments was given according to the standard institutional protocol and patients were followed according to the actual institutional guidelines.

Results: Between August 2002 and June 2009, 474 SLN+ patients were randomized to completion ALND (arm A-standard treatment, 244 patients) or RNI (arm B-investigational treatment, 230 patients). There were no significant differences in terms of major prognostic factors between the two arms. Two-hundred and fourty-two patients (99.6%) on arm A and 229 patients (99.6%) on arm B received adjuvant systemic treatments including chemotherapy and/or endocrine treatment (p=NS). One-hundred and ninety-four patients (79.5%) received adjuvant chemotherapy on arm A and 159 patients (69.1%) on arm B (p=0.031). Two-hundred and four patients (83.6%) received adjuvant endocrine treatment on arm A and 196 patients (85.2%) on arm B (p=NS). Six patients (2.5%) received adjuvant trastuzumab treatment on arm A and 13 patients (5.7%) on arm B (p=NS).

Conclusions: The result of completion ALND after positive SLNB appears to have no major impact on the administration of adjuvant systemic therapy.

Keywords: breast cancer, positive sentinel lymph node, regional nodal irradiation, adjuvant chemotherapy

Introduction

The primary site of lymphatic drainage of the breast is the axillary region. Axillary lymph node metastasis in patients with early-stage breast cancer is the most important prognostic factor for recurrence and survival and it also forms the basis for important therapeutic decisions [1].

For a century, axillary dissection (ALND) has been an essential component of the staging and axillary control of all breast cancer. In the mid-1990s the standard of surgical practice has moved from complete (level I–III) ALND to sampling level I and II lymph nodes, to the most recent trend performing axillary sentinel lymph node biopsy (SLNB). Patients without clinical involvement of the axilla should undergo SLNB routinely, and no additional lymph node surgery is needed when the sentinel node is disease-free [2–4].

Although current guidelines recommend completion ALND when the SLN(s) is positive, the need for completion ALND has been questioned. Among SLN positive patients about half have metastases in the remaining non-SLN(s), and completion ALND is still considered to be the standard care in this setting. On the other hand, another 50% of patients have no further involved nodes and would not be expected to benefit from ALND [5–8].

There may be a low-risk subgroup of SLN positive patients in whom CALND can be safely omitted. Emerging clinical data suggest that those factors which predict metastases to the non-SLN are the same as those that predict metastases to the SLN: tumor size, tumor grade, and lymphovascular invasion [9]. For patients with breast cancer, SLNB affords decreased morbility compared with ALND, including a lower rate of lymphedema, seromas, pain and sensory changes [10–11].

An acceptable less invasive alternative for ALND in the case of positive SLNB could be regional nodal irradiation (RNI) covering the axillary tail. In a series of randomized clinical trials no difference was found between ALND and axillary radiation therapy in regional control, survival, and long-term morbidity for early-stage breast cancer [12].

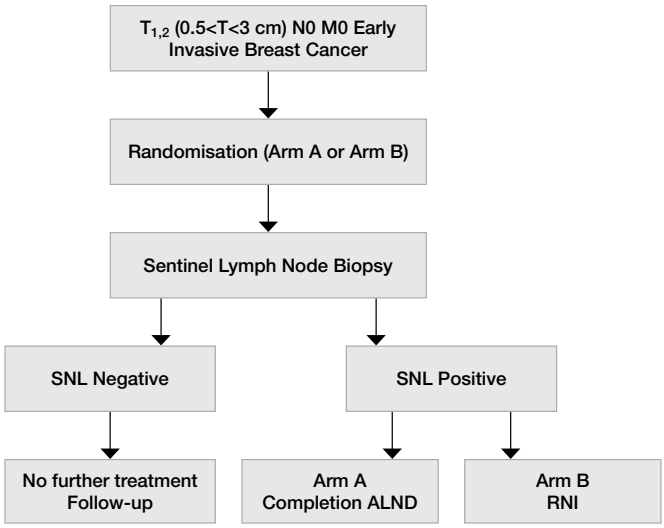

Fig. 1. Study design. Patients with primary invasive breast tumors less then 3 cm in diameter and clinically negative axillary lymph nodes were randomly assigned to one of the two treatment arms. If the SLNB came up as positive, then patients in group B received postoperative regional nodal irradiation (RNI) without axillary lymph node dissection (ALND), while those in group A received standard care (completion ALND).

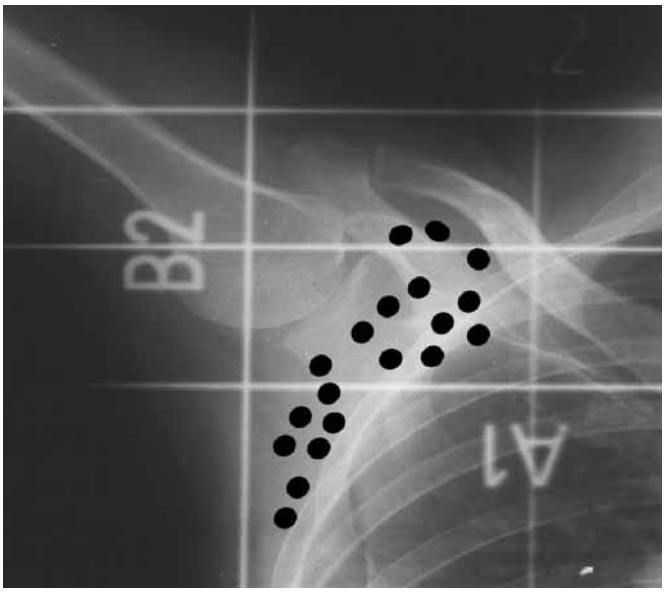

Fig. 2. Patients allocated to the ANI arm were irradiated after surgery. All three levels of the axilla and the supraclavicular fossa were considered target volume. Level I axillary nodes were covered by breast/chest-wall tangents.

Patients and methods

The Hungarian National Institute of Oncology started the OTOASOR trial in 2002. This phase III randomized clinical trial compares CALND versusRNI in early-stage breast cancer patients with positive SLN. All patients with clinically negative lymph nodes were randomly assigned to ALND or RNI before the SLNB procedure. However, only patients with positive SLNs were treated according to their random assigment arm. The main objective of the trial is to prove equivalent survival and locoregional control for patients with axillary lymph node metastasis by SLNB with reduced morbidity if treated with RNI instead of CALND. The study design and patients flow chart of the OTOASOR trial are shown in Figure 1.

The trial was approved by the National Institute of Oncology's Ethical Committee, and informed consent was obtained for the patients. The patients included in the trial were women with primary invasive breast tumors clinically less then 3 cm in diameter and no axillary lymphadenopathy. Exclusion criteria included: age over 75 years or life expectancy without cancer less than 5 years, non-infiltrating carcinoma, previous excision biopsy of the breast, primary chemo and/or endocrine treatment, and pregnancy. Furthermore patients with breast tumor over 3 cm or with clinically evident metastatic involvement of the axilla were also excluded. All patients had preoperative triple diagnosis along with routine blood tests with tumor markers. Until June 2009, a total of 2,106 patients have been included to the OTOASOR trial.

Surgery

Breast-conserving surgery or mastectomy was performed for all patients according to our current surgical protocols. If the primary tumor was not palpable the radio-guided occult lesion localization (ROLL) procedure was performed to detect the tumor. The SLNB procedure was performed using the combined method of patent blue dye and technecium (^{99}Tc) isotope, but in the last four years of the trial we used only the isotope method to detect SLN(s). The patent blue stain was used only, when the SLN(s) were not performed on the lymphoscintigrams. During surgery we used a gamma probe to detect SLN(s). All radioactive and blue-stained SLN(s) were removed together with all lymph nodes that were suspicious for metastatic by palpation. Patients who were assigned to the ALND arm underwent level I–II CALND during the first operation if the imprint cytology was positive for the removed SLN(s). When the SLNs were found to be positive solely by immunohistochemistry or hematoxylin-eosin staining, the patients underwent CALND within 4–6 weeks. Removal of at least six lymph nodes was mandatory. Those patients who were allocated to the RNI arm underwent no further axillary surgical procedure. Extra-axillary SLN(s) was(were) not removed.

Pathology

Breast tumor pathological work-up was done according to the routine institutional guidelines (data on tumour type, tumour size, excision margins, histological and nuclear grade, ER, PR and HER2 status with immunohistochemistry and/or FISH were given). During SLNB intraoperative imprint cytology was performed routinely for patients randomized to the ALND arm. The SLNs were finally processed for histology by serial sectioning (0.5 mm levels) and hematoxylin and eosin (HE) staining but no immunohistochemistry. All negative SLNs were investigat-

Table I. Basic characteristics of patients by treatment arms

Characteristic	Arm A (ALND) (N=244) n (%)	Arm B (RNI) (N=230) n (%)
Age (years)		
Median	54.7	55.2
Range	26–74	27–74
Menopausal status		
Pre	83 (34)	62 (27)
Post	161 (66)	168 (73)
Tumor side		
Right	129 (53)	102 (44)
Left	115 (47)	128 (56)
Surgery		
BCS	211 (86)	199 (87)
Mastectomy	33 (14)	31 (13)
pT stage		
pT1a	1 (0.4)	1 (0.4)
pT1b	16 (6)	18 (8)
pT1c	88 (38)	119 (52)
pT2	123 (50)	87 (38)
pT3	16 (6)	5 (2)
Hystology		
Ductal	193 (79)	188 (82)
Lobular	40 (16)	28 (12)
Other	11 (5)	14 (6)
Grade		
I	38 (16)	50 (22)
II	125 (51)	111 (48)
III	81 (33)	69 (30)
ER status		
Positive	203 (83)	192 (83)
Negative	41 (17)	38 (17)
PR status		
Positive	174 (71)	158 (69)
Negative	70 (29)	72 (31)
HER-2		
Positive	17 (7)	29 (13)
Negative	227 (93)	201 (87)

ALND = axillary lymph node dissection; RNI = regional nodal irradiation; BCS = breast-conserving surgery; ER = estrogen receptor; PR = progesterone receptor

ed further by immunohistochemistry with a cytokeratin cocktail and epithelial membrane antigen. Tumor deposits were categorized as macrometastases (>2 mm), micrometastases (0.2 to 2 mm) or isolated tumor cells (≤0.2 mm).

Radiotherapy and adjuvant systemic therapy

Patients after breast-conserving surgery underwent postoperative radiotherapy to the remaining breast tissue and the tumor-bed according to the standard institutional radiotherapy protocols. Patients with positive SLN(s) allocated to the RNI arm were irradiated within 8 weeks after surgery. All three levels of the axilla and the supraclavicular fossa were considered target volume (Figure 2). The dose of RNI was 50 Gy in 25 fractions of 2 Gy, 5 days a week. Postoperative RNI in patients undergoing ALND was allowed in patients with four or more tumor-positive nodes (pN2a or pN3a). Patients were treated with adjuvant systemic therapy according to standard institutional protocols. Adjuvant trastuzumab treatment has been available since January 2008 in our Institute.

Table II. Administration of adjuvant therapy by treatment arms

Adjuvant systemic therapy	Arm A (ALND) (N=244) n (%)	Arm B (RNI) (N=230) n (%)
ET alone	7 (3)	0 (0)
CT alone	2 (1)	0 (0)
CT+RT+ET	156 (64)	133 (58)
RT+ET	43 (18)	71 (31)
CT+RT	30 (12)	26 (11)
CT+ET	6 (2)	NA
Type of radiotherapy		
Breast RT	211 (86)	199 (87)
Chest-wall RT	21 (0.9)	9 (0.4)
RNI	76 (31)	230 (100)

ALND = axillary lymph node dissection; RNI = regional nodal irradiation; ET = endocrine therapy; CT = chemotherapy; RT = radiotherapy

Patient's follow-up was recommended according to the actual institutional guideline.

Results

In total of 2,106 patients were randomized for CALND (arm A-standard treatment, 1,054 patients) or RNI (arm B-investigational treatment, 1,052 patients). SLN was not identified in 33 patients (1.6%), 15 patients (1.4%) on arm A, and 18 patients (1.7%) on arm B, these patients were excluded and had ALND. SLN was identified in 2,073 patients (98.4%), 1,039 patients on arm A and 1,034 patients on arm B. SLN was positive in 526 patients (25.4%). Overall, 52 SLN-positive patients were excluded from the study because of protocol violation or patient's preference (17 from arm A and 35 from arm B). There were no significant differences in terms of major prognostic factors between the ALND and ANI arms. Basic characteristics of patients are listed in Table I. Overall 242 patients (99.6%) on arm A and 229 patients (99.6%) on arm B received adjuvant systemic treatment including chemo- and/or endocrine therapy (p=NS; see Table II.). In the ALND arm 194 patients (79.5%) received chemotherapy and 159 patients (69.1%) on the RNI arm (p=0.031). Two-hundred and four patients (83.6%) received adjuvant endocrine treatment on arm A and 196 patients (85.2%) on arm B (p=NS). Six patients (2.5%) received adjuvant trastuzumab treatment on arm A and 13 patients (5.7%) on arm B (p=NS).

Discussion

In the present work we intended to investigate, whether the result of cALND influence the recommendation for adjuvant treatment in SLN+ patients, after they was treated with adjuvant RNI instead of ALND. This study shows no difference in the administration of adjuvant systemic therapy between the two treatment groups of the OTOASOR trial of the Hungarian National Institute of Oncology, which randomly assigned patients with SLN positive breast cancer between ALND and RNI. The proportion of patients having 4 or more positive lymph nodes in the ALND arm is low (15%), and all these patients are classified as high-risk. Although SLNB provides

information only on the status of the SLNs, and further axillary nodal involvement remaines unknown, the extent of nonSLN(s) involvement in the RNI arm does not affect the administration of adjuvant systemic therapy.

Conclusions

Our preliminary data of our OTOASOR trial suggest that RNI without ALND does not increase the risk of axillary failure in SLN+ patients. The result of our study suggests that the extent of nodal involvement in the RNI arm does not affect the administration of adjuvant systemic therapy. These results support the hypothesis that the need for adjuvant chemotherapy is mainly based on tumor and patient characteristics or SLN status, and the knowledge of further axillary nodal involvement is not mandatory. In addition, long-term clinical results are highly awaited from the relevant well-known randomized clinical trials (Z0011, AMAROS and OTOASOR) evaluating the role of SLNB, ALND and RNI in the management of early-stage breast cancer patients.

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