e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2021, Volume 26, Number 5, pages: 785–792
DOI: 10.5603/RPOR.a2021.0101
Received: 17.03.2021
Accepted: 14.09.2021

Molecular type and maximal metastasis diameter influence risk of axillary recurrence in breast cancer patients after positive sentinel lymph node biopsy

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ABSTRACT

Background: Breast cancer patients with positive sentinel lymph node biopsy (SLNB) may be spared axillary lymph node dissection (ALND) in favour of irradiation. The aim of the study was to estimate local control probability in the axilla (axLCP).

Materials and methods: We identified 1832 invasive breast cancer patients who had undergone SLNB at our centre. We measured maximal metastasis diameter (SLDmax) in the sentinel lymph nodes and lymph node metastasis volume (VALN) from ALND in 246 patients with one or two positive SLNs. We calculated axLCP after irradiation and systemic treatment for different molecular types.

Results: VALN values are higher for high grade tumours and larger metastases in SLNs (> 5 mm). It is smaller in luminal A tumours. axLCP is high, nearly 100%, in all molecular types in radiation sensitive tumours (SF2 Gy = 0.45), except luminal B. Expected axLCP is relatively low (67%) in luminal B radiation sensitive tumours with no chemotherapy and nearly 100% with chemotherapy.

Conclusion: VALN values differ among molecular tumour types. They depend on SLNDmax and tumour grade. New prognostic factors are needed for selected luminal B breast cancer patients (i.e. high grade tumours, large metastases in SLNs) after positive SLNB intended to be spared ALND and chemotherapy.

Key words: breast cancer; sentinel lymph node; radiotherapy; axillary lymph node dissection; prognostic factor

Rep Pract Oncol Radiother 2021;26(5):785–792

Introduction

Sentinel lymph node biopsy (SLNB) is an important procedure in the management of breast cancer patients with clinically negative ipsilateral axillary lymph nodes. Multiple trials show that axillary lymph node dissection (ALND) and irradiation are unnecessary if there is either no metastasis [1, 2] or micrometastasis [3, 4] in the resected sentinel lymph node (SLN).

Two randomised trials, ACOSOG Z011 and AMAROS, compared ALND and axillary irradiation in patients with metastasis in SLN [5, 6]. In both trials, nearly 60% of enrolled patients had macrometastases in one or two SLNs. The results did not differ significantly if either ALND or irradiation were implemented. Irradiation used instead of ALND leads to lower toxicity because fewer patients have arm lymphoedema [4, 6] and neuropathy [4]. Following the results of these trials, the recommenda-

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tions suggest applying irradiation to the ipsilateral axillary fossa and avoiding ALND in breast cancer patients with pT1–2 tumours with no prior systemic treatment and metastases in 1–2 SLNs [7, 8].

Almost two-thirds of patients in the ACOSOG Z011 and AMAROS trials underwent chemotherapy [5, 6]. Based on current standards, chemotherapy is recommended for breast cancer patients with Her-2/neu overexpression and triple-negative tumours, and for a selected group of patients with luminal-type tumours and involved axillary lymph nodes [7, 8]. Patients with luminal-type tumours and three or less involved axillary lymph nodes should be qualified to chemotherapy following multigene assay risk factor analysis [7]. Based on current standards, less breast cancer patients are offered chemotherapy.

Information on tumour biology in the ACOSOG Z011 and AMAROS trials is limited. The ACOSOG Z011 trial reported information only on oestrogen receptor (ER) positivity (nearly 82% of patients) [5, 6]. In an earlier publication, we presented data that showed significant differences in the tumour volume in the axillary lymph nodes after positive SLNB in different breast cancer molecular types (luminal A vs. luminal B vs. triple-negative vs. Her-2/neu overexpression) [9].

The aim of this study was to estimate local control probability after axillary irradiation without ALND in different treatment scenarios for different molecular subtypes (Luminal A vs Luminal B vs triple negative vs Her-2/neu overexpression tumours), use of systemic treatment methods (hormonal treatment, chemotherapy) and levels of radiation sensitivity in breast cancer patients macrometastses in 1 or 2 SLNs.

Materials and methods

Between May 2006 and December 2013 we identified 1832 invasive breast cancer patients who had undergone the SLNB procedure at our centre. All patients underwent operation as a primary procedure. Ultrasound examination of the axilla was performed in every patient before operation. One to nine sentinel lymph nodes per patient were resected (mean value 1.8, median 1). In the analysed cohort positive SLNs (metastatic) were detected in 451 cases (24.6%). Sixty patients did not undergo axillary lymphadenectomy despite the fact that the metastases were present in resected SLNs, due to patient refusal. In 20 (33.3%) cases there were micrometastases in SLNs and macrometastases were present in 40 (66.6%) cases. Those with macrometastases underwent adjuvant irradiation according to results of ACOSOG Z011 trial results [5]. Three hundred ninety-one patients from the SLN-positive group additionally underwent ALND, and in 157 cases (40.2%) further positive lymph nodes (metastatic) were present.

The specimens of those 391 patients were further analysed. An experienced pathologist reviewed lymph node specimens from SLN-positive cases and lymph node specimens after ALND. For each patient, reference specimens of positive SLNs and ALNs were selected. The specimens were scanned with an AperioScanScope AT Turbo scanner (Aperio, Vista, CA, USA). In 323 cases (82.6%), we were able to gather images for the sentinel and axillary lymph nodes. Percentage of lost data was comparable in both groups with and without metastases to the axillary lymph nodes (19.8% vs 15.9%). We excluded from analysis 64 cases (19.9%) with micrometastases in SLNs and 13 cases (4%) with macrometastases in 3 or more SLNs. The analysis was further conducted on remaining 246 cases (76.1%) with macrometastses in 1 or 2 SLNs.

Scanned images of lymph nodes were further analysed with the AperioImageScope software (Aperio, Vista, CA, USA). Areas of tumour foci were contoured and the surface of infiltration for every field was calculated. Based on the circle area formula ($A = \pi r^2$), the radius for every tumour focus was calculated and volume estimated ($V = {}^4/_3\pi r^3$). Volumes of tumour foci were then summed in each case (every patient separately for the sentinel and axillary lymph nodes). Finally we obtained tumour volume in the remaining axillary lymph nodes (V_{ALN}, expressed in mm^3) and metastasis diameter in SLNs (SLN_{Dmax}, expressed in mm) for 246 breast cancer patients with macrometastases in one or two SLNs.

An independent-sample *t*-test was used to compare mean V_{ALN} values for different risk factors (Tab. 1). Those factors were age (≤ 40 y *vs.* 40–60 y *vs.* ≥ 60 y), tumour size (pT1a–b *vs.* pT1c *vs.* pT2), tumour type (NST grade I, tubular vs. NST grade II vs. NST grade III *vs.* Lobular cancer), ER receptor (present *vs.* negative), Her2/neu receptor (no *vs.* overexpression), molecular type (luminal

Table 1. Correlation of mean VALN and selected predictive factors

	Number	Mean V_{ALN}
Age		
≤ 40 y	14	70.84 (–8.3–149.99)
> 40 y < 60 y	141	132.3 (59–205.63)
≥ 60 y	91	163.88 (43.84–283.92)
≤ 40y *vs.* > 40y < 60y, NS; > 40y < 60y *vs.* ≥ 60y, NS; ≤ 40y vs ≥ 60y, NS		
Tumour size		
pT1a-b	28	15.36 (–4.98–35.7)
pT1c	128	125.32 (44.48–206.17)
pT2	87	207.89 (83.49–332.3)
pT1a-b *vs.* pT1c, NS; pT1a-b *vs.* pT2, NS; pT1c *vs.* pT2, NS		
Tumour type		
NST I,t	19	13.12 (–12.51–38.74)
NST II	115	61.96 (33.17–90.76)
NST III	65	301.98 (113.75–490.21)
Lobular	39	99.07 (19.5–178.64)
NST I,t *vs.* NST II, NS; NST I,t *vs.* NST III, NS; NST III *vs.* lobular, NS; NST II *vs.* NST III, p = 0.0013		
ER		
Positive	203	121.87 (59.12–184.62)
Negative	41	239.48 (43.72–435.25)
Positive *vs.* Negative, NS		
Her2/neu		
No	205	137.34 (65.79–208.89)
Yes	37	173.09 (89.96–256.22)
No *vs.* Yes, NS		
Molecular type		
Luminal A	90	30.17 (7.01–53.34)
Luminal B	73	263.74 (95.83–431.65)
Her2/neu overexpression	37	173.09 (89.96–256.22)
TNBC	24	233.75 (–93.82–561.33)
Luminal A *vs.* luminal B, p = 0.0028; luminal A *vs.* Her2/neu overexpression, p < 0.0001; luminal A *vs.* TNBC, p = 0.0168; Luminal B *vs.* Her2/neu overexpression, NS; luminal B *vs.* TNBC, NS; Her2/neu overexpression *vs.* TNBC, NS		
SLN+		
1	196	130.4 (64.45–196.36)
2	50	180 (24.93–335.06)
1 *vs.* 2, NS		
ECE		
No	132	94.46 (41.09–147.83)
Yes	114	193.77 (77.67–309.88)
No *vs.* Yes, NS		
SLN_{Dmax}		
2–5 mm	96	50.21 (19.89–80.53)
> 5 mm	150	198.26 (101.11–295.41)
2–5 mm *vs.* > 5 mm, p = 0.019		

V_{ALN} — tumour volume in remaining axillary lymph nodes [mm^3]; pT1a-b — primary tumour diameter < 10 mm; pTc — primary tumour diameter 10–20 mm; pT2 — primary tumour diameter >20 mm; NST I —t — no special type grade 1 and tubular cancer; NST II — no special type grade 2; NST III — no special type grade 3; ER — oestrogen receptor; Her2/neu — Her2/neu receptor overexpression; SLN+ — number of positive sentinel lymph nodes; ECE — extracapsular extension; SLN_{Dmax} — maximal diameter of metastasis in sentinel lymph node

A *vs.* luminal B *vs.* Her2/neu overexpression *vs.* triple-negative breast cancer), number of involved SLN (1 *vs.* 2), SLN extracapsular extension (no *vs.* yes), and SLN_{Dmax} (2–5 mm *vs.* >5 mm). The difference was significant if the p value was less than 0.05.

We defined luminal tumours as those with oestrogen and progesterone receptors with no Her-2/neu receptor overexpression. Those with proliferative index value above median or progesterone receptors level below 20% or high grade were defined as luminal B. Her2/neu overexpression breast cancers were those with receptor overexpression in either immunochemistry or genetic testing. Those with neither expression of hormonal nor Her-2/neu receptors were defined as triple negative breast cancers.

Statistical analyses were performed using MedCalc for Windows, version 14.10.2 (MedCalc Software, Ostend, Belgium).

We calculated the local control probability (LCP) in the ALN for different molecular types (Tab. 2). For every patient the values of V_{ALN} were converted into the number of cancer cells (N_{BC}) based on formula that 1 mm^3 tumour harbours 10^6 cancer cells [10].

$$N_{BC} = V_{ALN} \times 10^6$$

We considered that all patients with Her2/neu overexpression and triple-negative breast cancer would undergo chemotherapy and we defined that the treatment leads to a decrease in number of cancer cells by a factor of 10^3, and for those with luminal A and B tumours, the decrease was set at 10^2. The number of cells surviving chemotherapy (N_{chBC}) were calculated following the formulas below:

Chemotherapy TNBC or Her2/neu overexpression:

$$N_{chBC} = N_{BC} \times 10^{-3}$$

Chemotherapy luminal A or B tumours:

$$N_{chBC} = N_{BC} \times 10^{-2}$$

No chemotherapy:

$$N_{chBC} = N_{BC}$$

Classical fractionation scheme of postoperative irradiation is 25 fractions of 2 Gy per fraction. 2 Gy surviving fraction (SF_{2Gy}) expresses percentage of cancer cells surviving one fraction of 2 Gy irradiation. We set it at 0.45. Following

Table 2. Local control probability in axilla for different molecular types and after division into low and high-risk luminal breast cancers

Molecular type		Mean V_{ALN}	N_{BC}	CHth	N_{chBC}	SF_{2Gy} = 0.45[e]	N	LCP	HTH	axLCP
Luminal A	90	30.17 (7.01–53.34)	3.01×10^7	No	3.01×10^7	2.14×10^{-9}	6.44×10^{-2}	93.8%	10%	99.9%
Luminal B	73	263.74 (95.83–431.65)	2.63×10^8	No	2.63×10^8	2.14×10^{-9}	5.63×10^{-1}	57%	10%	67%
Luminal B	73	263.74 (95.83–431.65)	2.63×10^8	Yes	2.63×10^6	2.14×10^{-9}	5.63×10^{-3}	99.4%	10%	99.9%
Her2/neu overexpression	37	173.09 (89.96–256.22)	1.73×10^8	Yes	1.73×10^5	2.14×10^{-9}	3.7×10^{-4}	99.9%	No	99.9%
Her2/neu overexpression	37	173.09 (89.96–256.22)	1.73×10^8	No	1.73×10^8	2.14×10^{-9}	3.7×10^{-1}	69.1%	Yes	79.1%
Her2/neu overexpression	37	173.09 (89.96–256.22)	1.73×10^8	No	1.73×10^8	2.14×10^{-9}	3.7×10^{-1}	69.1%	No	69.1%
TNBC	24	233.75 (–93.82–561.33)	2.33×10^8	Yes	2.33×10^5	2.14×10^{-9}	4.99×10^{-4}	99.9%	No	99.9%
TNBC	24	233.75 (–93.82–561.33)	2.33×10^8	No	2.33×10^8	2.14×10^{-9}	4.99×10^{-1}	60.7%	No	60.7%

V_{ALN} — tumour volume in remaining axillary lymph nodes (mm^3); N_{BC} — number of breast cancer cells correlated with tumour volume (VALN = 1 cm^3 harbours 10^6 breast cancer cells); CHth — chemotherapy; N_{chBC} — number of breast cancer cells after chemotherapy (depleted by 10^3 for Her2/neu overexpression and triple negative breast cancer, by 10^2 for luminal tumours); SF2Gy = 0.45 — depletion level of breast cancer cells number for 2Gy surviving fraction equal to 0.45; N — mean number of cancer cells in axilla after chemotherapy and irradiation; LCP — local control probability in axilla following chemotherapy and radiotherapy, calculated using the formula LCP = e^{-N}; HTH — hormonotherapy and its influence on LCP; axLCP — local control probability in axilla for surviving fraction 2 Gy equal to 0.45; TNBC — triple negative breast cancer

Table 3. Local control probability in axilla for different molecular types and different radiation sensitivity values

Molecular type		Mean V_{ALN}	N_{BC}	Chth	HTH	axLCP (SF = 0.45)[e]	axLCP (SF = 0.5)	axLCP (SF = 0.6)
Luminal A	90	30.17 (7.01–53.34)	3.01×10^7	No	Yes	99.9%	50.9%	10%
Luminal B	73	263.74 (95.83–431.65)	2.63×10^8	No	Yes	67%	10%	10%
Luminal B	73	263.74 (95.83–431.65)	2.63×10^8	Yes	Yes	99.9%	99.9%	10%
Her2/neu overexpression	37	173.09 (89.96–256.22)	1.73×10^8	Yes	No	99.9%	99.5%	61.3%
TNBC	24	233.75 (–93.82–561.33)	2.33×10^8	Yes	No	99.9%	99.3%	51.2%

V_{ALN} — tumour volume in remaining axillary lymph nodes; N_{BC} — number of breast cancer cells correlated with tumour volume (VALN = 1 cm^3 harbours 10^6 breast cancer cells); CHth — chemotherapy; HTH — hormonal treatment; axLCP(SF=0.45) — local control probability in axilla for surviving fraction 2 Gy equal to 0.45; axLCP(SF=0.5) — local control probability in axilla for surviving fraction 2 Gy equal to 0.5; axLCP(SF=0.6) — local control probability in axilla for surviving fraction 2 Gy equal to 0.6; TNBC — triple negative breast cancer

the above assumption the number of cancer cells in tumour is reduced by 0.45[25] and it is 2.14×10^9. Twenty-five 2 Gy fractions reduce the number of cancer cells by a factor of 2.14×10^9. The mean number of surviving cancer cells (N) is expressed by the formula:

$$N = N_{chBC} \times 2.14 \times 10^{-9}$$

The risk of relapse (LCP) in the axilla depends on N value and is expressed by the formula:

$$LCP = e^{-N}$$

For those patients with the presence of positive oestrogen receptors in the tumour, we calculated the expected local control probability in the axilla (axLCP) by increasing the final value by 10%.

Following presented methodology we calculated axLCP for moderately sensitive tumours ($SF_{2Gy} = 0.5$) and radiation resistant ones ($SF_{2Gy} = 0.6$) (Tab. 3).

Results

V_{ALN} mean values differed significantly among NST grade II and grade III tumour types (p = 0.0013), SLN_{Dmax} 2–5 mm *vs.* > 5 mm (p = 0.019), luminal A *vs.* luminal B (p = 0.0028), Her2/neu overexpression (p < 0.0001), and triple-negative breast cancer (p = 0.0168). The were no significant differences among different tumour diameters, NST grade I, lobular type, and other higher-grade NST tumours. ER and Her2/neu status did not impact mean V_{ALN} values. Luminal B, Her2/neu overexpression, and triple-negative breast cancers did not differ significantly. The same result was observed for the number of involved SLNs and extracapsular extension (Tab. 1).

In radiation sensitive tumours ($SF_{2Gy} = 0.45$) axLCP for Her-2/neu overexpression and triple-negative breast cancers is nearly 100% if chemotherapy and irradiation of the ALN is used after a positive SLNB, but with no chemotherapy it is only 69.1% (79.1% with hormonal treatment) in Her2/neu overexpression and 60.7% in TNBC. For luminal A tumours axLCP is nearly 100% if irradiation and hormonal treatment is used. In luminal B tumours axLCP is 67% with irradiation and hormonal treatment only and increases to nearly 100% for chemotherapy use (Tab. 2).

In moderately sensitive tumours the axLCP is high, nearly 100%, for Her-2/neu overexpression, triple-negative and luminal B breast cancers if chemotherapy and radiotherapy is used. For luminal A it drops to nearly 50% if only radiotherapy and hormonal treatment is used (Tab. 3). In radiation resistant tumours the axLCP values are low for all tumour types (from 10% for luminal tumours to 61.3% for Her-2/neu overexpression) (Tab. 3).

Discussion

In the present study, we showed that V_{ALN} is correlated with the molecular type, high grade, and SLN_{Dmax} after positive SLNB. V_{ALN} is a predictive factor for locoregional treatment results that are reflected by axLCP. It is also influenced by radiation sensitivity, systemic treatment (chemotherapy, hormonal treatment), and irradiation (dose, fractionation). A combined effect of those factors resulted in a low axillary recurrence rate in the ACOSOG Z0011 and AMAROS trials (1.5% and 1.19%, respectively) [5, 6]. Breast cancer patients with mac-

rometastases in one or two SLNs may be spared ALND in favour of irradiation, based on the results of those trials [7, 8].

In both trials, one or two positive SLNs were present in nearly 60% of enrolled breast cancer patients. Considering that 40% of all patients had micrometastases or isolated tumour cells in SLNs and that two-thirds of all enrolled patients underwent chemotherapy, it is possible that most patients with one or two positive SLNs underwent chemotherapy. The current recommendations lead to less frequent use of chemotherapy in luminal-type breast cancer patients with metastases in 1–3 axillary lymph nodes [7, 8]. There are no data whether less frequent use of chemotherapy influences local treatment results in patients with metastases in 1–2 SLNs. There are limited data on predictive factors for the pathological stage pN2 or pN3 after ALND that follows a positive SLNB [11, 12].

Based on current recommendations for chemotherapy use, we estimated axLCP. The calculations were based on mean values of V_{ALN} and molecular types of breast cancer. We made some assumptions. We assumed that chemotherapy decreases the number of breast cancer cells by a factor of 10^3 in non-luminal types and by a factor of 10^2 in luminal types of tumours. Schipper et al. [13] analysed the frequency of axillary lymph node pathological complete remission in the group of patients who had undergone neoadjuvant chemotherapy without or with trastuzumab (for Her-2 receptor overexpression). They reported a 50% pathological complete remission rate for triple-negative tumours and 47.5–56.6% for those with Her-2 receptor overexpression. There was only 15.4% of axillary lymph nodes complete pathological remission in luminal-type tumours [13]. One cm^3 mass is thought to be occupied by 10^9 cells, as subclinical disease is occupied by no more than 10^6 cancer cells [10]. The probability of local control (P) depends on the mean value of the surviving clonogen cells (N): $P = e^{-N}$. Then N may be calculated: $N = \ln_P$ Given that 50% pathological complete remission occurs after chemotherapy in non-luminal tumours, and 15% occurs for luminal tumours, the N value was 0.69 for non-luminal and 1.89 for luminal tumours. The estimated mean number of clonogen cells before chemotherapy (10^4–10^5) allows estimation of the decrease of the mean N value by a factor 10^3 for triple-negative, Her-2/neu overexpressing tumours, and 10^2 for luminal-type tumours.

We assumed that hormonal treatment increases predicted axLCP by 10%. Wazer et al. [14] reported that adding tamoxifen to irradiation improved 10-y local control by 91.6% to 98.1% in breast cancer patients who had undergone breast conserving surgery. In a comparable group, Bucholz et al. [15] showed improved 8-y local control (95.6% *vs.* 85.2%) in patients who had undergone systemic treatment compared to those who had been spared it.

Ruka et al. [16] estimated the radiosensitivity of breast cancer cells. It was expressed by the number of cells surviving a dose of 2 Gy (SF_{2Gy}). The obtained values ranged from 0.23 to 0.54 (mean 0.38). Speers et al. [17] showed no difference in the SF_{2Gy} value among different molecular types of breast cancer, with values ranging from 17% to 77%. They defined tumours with SF_{2Gy} 0.45 or below to be radiation sensitive [18]. For the purpose of this study, we set also the value of SF_{2Gy} to 0.45 for radiation sensitive tumours, which means that 45% of breast cancer cells survive every fraction of 2-Gy irradiation. The common fractionation scheme is 25 daily doses of 2 Gy. The mean number of surviving clonogen cells (N) is expressed by the formula $N = 0.45^{25}$, and the value obtained was 2.14×10^{-9}.

One may discuss whether the assumptions we make are reliable. The study is not intended to draw final conclusions. The relationships we present are significant in selected prognostic factors. V_{ALN} values are higher for high grade tumours and larger metastases in SLNs. V_{ALN} is smaller for luminal A tumours.

The number of axillary relapses was low in the ACOSOG Z0011 and AMAROS trials [5, 6]. Nevertheless, it does not allow us to resign searching for risk factors of relapses. Almost 50% of patients with axillary recurrences after negative sentinel lymph node biopsy develop distant metastases and only 58% survive 5 years since relapse [18]. Selecting those who benefit from ALND may be important. Expected axLCP suggests that the number of those who might benefit from ALND is small.

Following present recommendations, most breast cancer patients with clinically negative axilla and either triple negative or Her-2/neu overexpressing tumours are going to be given neoadjuvant systemic treatment [7, 8]. Nowadays, the ACOSOG

Z0011 and AMAROS trials considerations rarely apply to those patients. Luminal A tumours are radiation sensitive as presented in the study by Laurberg et al. [19]. They analysed data from two independent post-mastectomy trials (British Columbia and Danish Breast Cancer Cooperative Group 82b) and showed the biggest benefit from adjuvant radiotherapy in patients with luminal A type breast cancers. In this group of patients irradiation with hormonal treatment might be enough.

Breast cancer patients with luminal B tumours seem to be at the highest risk of relapse in the axilla if they are not given adjuvant chemotherapy. As we mentioned earlier, nowadays less luminal B patients are qualified for adjuvant chemotherapy, as not every patient with positive SLN is going to be in stage pN2 or pN3. In our group only 23 (31.5%) luminal B patients were pN2 or pN3. It seems we need additional prognostic factors in this group of patients to spare them ALND and adjuvant chemotherapy. Adjuvant irradiation and hormonal therapy might not be enough to prevent relapse in the axillary lymph nodes.

Conclusions

V_{ALN} values differ among molecular tumour types. They also depend on SLN_{Dmax} and tumour grade in patients with one or two macrometastases in SLN. We need new prognostic factors for selected luminal B breast cancer patients (i.e. high grade tumours, large metastases in SLNs) after positive SLNB intended to be spared ALND and chemotherapy.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

This article is a retrospective cohort data analysis of patients who were routinely treated in our institution in accordance with ethical standards of our institution and current medical knowledge.

Informed consent

There was no need to obtain informed consent from individual participants, because only retrospective data were analysed — available from hospital records.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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