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Receipt of adjuvant systemic therapy among patients with high-risk breast cancer detected by mammography screening

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Abstract *Background* Few studies have compared screen-detected (SD) breast cancer patients with symptomatic patients for the frequency and determinants of receipt of adjuvant systemic therapy according to accepted guidelines. *Methods* Depending on the date of diagnosis, adjuvant therapy guidelines from the 5th, 6th, and 7th St. Gallen International Conferences were used as standards to audit the treatment of 598 node-negative high-risk patients (59% SD) and 430 node-positive patients (40% SD) aged 50–69 years from an Italian cancer registry (1997–2001). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using backward stepwise logistic regression models. *Results* Among node-negative high-risk patients, SD cancers were smaller ($P = 0.000$) and of lower grade ($P = 0.003$). Downgrading was generally from grade 3 to grade 2, with an increased proportion of patients placed in the high-risk category due to grade 2 alone. The total rates of adjuvant systemic therapy were similar (58 vs. 60%) whereas SD patients were less often treated according to the guidelines (34 vs. 45%; OR = 0.61; 95% CI, 0.44–0.86). After adjustment for tumour size and other weaker confounders, the OR was 0.99 (95% CI, 0.67–1.46). Among node-positive patients, the OR of receiving the standard adjuvant systemic therapy did not differ between SD and symptomatic cancers. *Conclusions* SD cancers

amplified the prognostic heterogeneity of node-negative high-risk patients. Their lower likelihood of being treated according to the guidelines was largely explained by their lower risk profile. No evidence was found to suggest that physicians held a priori assumptions about the relative biological indolence of SD cancers.

Keywords Adjuvant systemic therapy · Breast cancer · Guidelines · Screening

Introduction

Many studies have shown that breast cancers detected by mammography screening have a lower malignant potential than symptomatic cancers. Screen-detected (SD) cancers are less likely to have axillary lymph node metastases, poor histological differentiation, high mitotic index, high S phase fraction, and low levels of hormone receptor expression [1–4]. Multivariate studies have associated SD cancers with a decreased risk of lymph node metastases even after adjustment for tumour size [1, 3], histological grade, hormone receptor status, and DNA ploidy [3]. Similarly, it has been observed that the lower stage of SD cancers does not entirely account for their lower proliferative activity [1].

In accordance with these findings, survival studies have demonstrated that the detection mode is an independent prognostic factor for breast cancer patients. Shen et al. [5] reported that detection by mammography screening is associated with a better disease-free survival adjusted for tumour size, lymph node status, and disease stage. In the study by Joensuu et al. [6], the benefit in disease-free survival for SD patients was independent of a larger set of known and putative prognostic factors, including tumour

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size in millimetres, tumour grade, hormone receptor status, cErbB2 amplification status, histological type, and number of metastatic axillary lymph nodes.

These observations suggest that the risk of distant metastases for patients with SD breast cancer may be overestimated unless the detection mode is taken into consideration [6]. By implication, since the detection mode is not accounted for in adjuvant systemic therapy guidelines, these may result in overtreatment of SD patients. Such a hypothesis has received attention in the last few years [7]. It has been suggested that detection by screening should be routinely recorded in future clinical trials. At present, however, there is insufficient evidence to suggest that this information should influence the choice of adjuvant therapy for breast cancer in clinical practice [7].

Whether SD patients are actually treated according to current standards is, however, virtually unknown. In some North American studies [8–10], they were less likely to receive chemo/hormone therapy than symptomatic patients, although adjustment for prognostic factors was incomplete. In Europe, some papers reported the frequency of adjuvant systemic therapy in consecutive series of SD patients without symptomatic controls [11, 12]. In a treatment audit of the British Breast Screening Programme, node-negative and node-positive patients were pooled [13]. Although a report from the Dutch screening programme stated that treatment approaches did not differ between SD and symptomatic patients after stratification by tumour stage, a detailed analysis was not presented [14].

The present paper reports a population-based study from northern Italy.

Methods

Objectives and rationale

The study considered the series of breast cancer patients registered by the population-based Romagna Cancer Registry between 1997 and 2001. Based on their date of publication, the recommendations of the 5th (1995), 6th (1998), and 7th (2001) St. Gallen International Conferences on Adjuvant Therapy of Primary Breast Cancer [15–17] were used as the standards against which to compare the treatment of patients undergoing surgery between January 1997 and November 1998, December 1998 and September 2001, and October and December 2001, respectively. Each set of recommendations was considered applicable starting from the month after publication.

To maintain a practical approach, the study focused on (1) node-negative patients at high risk (according to the 5th and 6th St. Gallen Conferences) or average/high risk (7th Conference) (herein cumulatively referred to as node-

negative high-risk patients), and (2) node-positive patients. The objective was to compare SD breast cancer patients with symptomatic patients for (1) the prognostic profile, (2) the total rate of adjuvant chemo/hormone therapy, and (3) the crude and adjusted likelihood of being treated according to the guidelines.

Setting

In the study area, organised mammography screening for women aged 50–69 years was gradually implemented between 1996 and 1997 [18]. All eligible women receive a personal appointment letter. Self-referral is accepted, provided that the woman is eligible. Current attendance rate is 72%. Follow-up investigations and treatment are free of charge. The screening service is supplied by the existing radiology departments and specialist mammography/breast clinics.

The study area is served by three National Health Service inpatient oncology departments, each with a day-hospital clinic, and four independent cancer day-hospitals. Private hospitals supply a marginal portion of surgical care for breast cancer, and do not offer medical oncology services. Cancer research and cancer treatment programmes in the area are coordinated by the Romagna Cancer Institute (IRST). The Unit of Biostatistics and Clinical Trials of the IRST confirmed that the guidelines from the 5th, 6th, and 7th St. Gallen Conferences were formally accepted without modification by all oncology departments and day-hospitals in the area, and were implemented within 1 month of publication.

Case series

In 1996, a few months before the start of the screening programme, female breast cancer registration at the Romagna Cancer Registry was modified. Standard registration items were supplemented with additional information on the detection mode, surgical treatment, tumour size, axillary lymph node status, tumour grade, estrogen and progesterone receptor (ER and PgR) status, and chemo/hormone therapy. For ER and PgR, the cut-off levels for positivity were obtained from the pathology and clinical chemistry laboratories in the area. Personnel from the Registry and the screening centres reviewed the mammography records of the registered breast cancer cases. The date of invitation, type of examination performed (screening following invitation, self-referral, assessment, diagnostic, follow-up), and the result were evaluated. According to the detection mode, the study cases were classified into five groups: prevalence-SD cancer; other SD cancer; interval cancer; cancer in non-attender; and cancer in woman not yet invited to take part in the screening programme. A SD cancer was defined as any cancer

diagnosed (1) after a positive mammography result, (2) following invitation or self-referral of an eligible asymptomatic woman to a screening centre, and (3) through programme-initiated assessment. Clinical personnel extracted systemic therapy data from inpatient hospital and day-hospital case records.

Between 1997 and 2001, a total of 4,459 invasive breast cancer patients were registered. For the purposes of the present study, patients with the following characteristics were excluded: age <50 years and >69 years ($n = 2,255$); residence in a health district where access to complete treatment data was not possible ($n = 397$); registration with death certificate only ($n = 4$); previous history of in situ or invasive breast cancer ($n = 70$); presurgical chemotherapy ($n = 19$); surgical treatment not performed ($n = 112$); ICD-O morphology code of phyllodes tumour, sarcoma, lymphoma, and leukaemia ($n = 7$); bilaterality ($n = 11$); distant metastases ($n = 2$); and loss to post-surgical follow-up ($n = 202$). A total of 1,380 cases of invasive, locoregional, surgically treated breast carcinoma were potentially eligible for the study.

Risk and treatment classification

Table 1 shows the recommendations of the 5th, 6th, and 7th St. Gallen Conferences for the adjuvant systemic therapy of postmenopausal patients with node-negative high-risk cancer (see a footnote to the Table for definition) and node-positive cancer. A set of working criteria was

Table 1 Summary of recommendations of the 5th, 6th, and 7th St. Gallen Conferences for adjuvant systemic therapy of postmenopausal patients with node-negative high-risk^a and node-positive breast cancer

Hormone receptor status	Conference		
	5th (1995)	6th (1998)	7th (2001)
ER-positive	TAM ^b	NA	NA
ER-negative	Chemo ^b	NA	NA
ER- or PgR-positive	NA	TAM + chemo ^c	TAM + chemo ^c
ER- and PgR-negative	NA	Chemo ^c	Chemo ^c

Modified from Goldhirsch et al. [15–17]

^a With tumour size >20 mm and/or tumour grade ≥ 2 and/or negative ER status (negative ER and PgR status, according to the 6th and 7th St. Gallen Conferences)

^b Treatment accepted for routine use

^c The use of tamoxifen alone was presented as a subordinate option that might be justified by considerations about a low relative risk of relapse, age, toxic effects, socioeconomic implications and patient preference. In the current study, this was not regarded as a standard treatment

ER = Estrogen receptor; PgR = Progesterone receptor; TAM = Tamoxifen; Chemo = Chemotherapy; NA = Not applicable

used for the risk and treatment classification of study patients. First, ER [15] and PgR [16, 17] status was categorized (1) assuming that tumours with focal weak positivity were positive, and (2) using the highest result in the event that the hormone receptors were determined using both biochemical and histochemical techniques.

Second, in the risk classification of lymph node-negative patients, the following criteria were adopted: (1) tumours with histological grade 2 were placed in the high risk category of guidelines from the 5th and 6th St. Gallen Conferences; (2) ER/PgR-positive tumours 1–2 cm in size with histological grade not reported were placed in the good or intermediate risk category of guidelines from the 5th and 6th Conferences; and (3) ER/PgR-positive tumours <1 cm in size with histological grade not reported, as well as grade 1 tumours <1 cm in size with ER/PgR status not reported or unknown were placed in the minimal (5th Conference) or minimal/low (6th and 7th Conferences) risk category.

Third, in comparing the observed treatment with the applicable guidelines, we assumed that: (1) all patients were postmenopausal; (2) hormone therapy plus chemotherapy was the standard treatment for node-negative high-risk patients and node-positive patients with ER/PgR status unknown [19]; (3) hormone therapy plus chemotherapy, but not hormone therapy alone, was the standard treatment for node-negative ER/PgR-positive patients in the 1998 and 2001 guidelines; and (4) any pattern of treatment was adequate for patients enrolled in trials of adjuvant chemo/hormone therapy [20].

Data analysis

None of the 1,380 potentially eligible patients had missing information on the detection mode. Prevalence-SD cancers and cancers detected in subsequent screens were pooled. All non-SD cancers were pooled as symptomatic cancers.

A total of 352 potentially eligible patients were excluded from analysis because they could not be classified as to lymph node status ($n = 20$ or 1.4%), could not be assigned to any risk category of node-negative cancers ($n = 59$ or 4.3%), were placed in the categories at minimal-low [15–17], good [15], and intermediate [16] risk ($n = 257$ or 18.6%), or had missing values for tumour size in millimetres ($n = 16$ or 1.2%). These exclusions were more frequent among SD patients ($n = 745$) than among symptomatic patients ($n = 635$). This reflected the greater prevalence of node-negative cancers at minimal-low, good, and intermediate risk (23.1 vs. 13.4%) among SD patients, whereas exclusions for missing or incomplete data on lymph node status, risk level, and tumour size had the same impact on both groups (6.8 vs. 6.9%).

One thousand and twenty-eight patients were available for analysis. A data quality check showed no appreciable

differences between SD ($n = 522$) and symptomatic patients ($n = 506$) with respect to the prevalence of missing information on tumour grade (8.2 vs. 12.3%) and hormone receptor status (24.3 vs. 23.7%).

The prognostic characteristics of patients were compared using the Mann–Whitney U test and the Pearson χ^2 test. Differences in the rates of adjuvant chemo/hormone therapy were tested using the Pearson χ^2 test and Mantel-Haenszel χ^2 test stratified by ER/PgR status.

The unadjusted odds ratio (OR) of SD patients being treated according to the guidelines and the 95% confidence interval (CI) were calculated. The OR was then modelled as a function of potential explanatory variables using a backward stepwise logistic regression model. The following covariates were initially included in the model: patient age (continuous); referral hospital (i.e., the place of surgical treatment) ($n = 6$); time period of diagnosis (i.e., the three above-mentioned time periods covered by the guidelines issued at the 5th, 6th, and 7th St. Gallen Conferences); ER/PgR status (negative, positive, unknown); tumour grade (1, 2, 3, unknown); tumour size (continuous); and—for node-positive patients alone—number of positive nodes (continuous). These variables were sequentially removed on the basis of the least significant contribution to the likelihood of the model. The detection mode was forced into each step.

Results

The 1,028 patients included in the analysis comprised 598 node-negative high-risk patients and 430 node-positive patients. Among these, there were 351 (58.7%) and 171 (39.8%) SD patients, respectively.

Node-negative high-risk patients detected by screening had a favourable distribution by tumour size and grade (Table 2). SD cancers were generally downgraded from grade 3 to grade 2. The proportion of tumours with grade ≥ 2 , however, was unchanged, which translated into an increased proportion of patients placed in the high-risk category due to tumour grade alone.

A favourable distribution by tumour size and grade was also observed among node-positive cancers detected by screening (Table 3). SD cancers had also a smaller median number of positive nodes.

The proportion of node-negative and node-positive patients receiving adjuvant systemic therapy is shown in Table 4. In both subgroups, the total rate of adjuvant chemo/hormone therapy was similar for symptomatic patients and SD patients. Conversely, a significantly smaller proportion of SD patients with negative lymph nodes were treated according to the applicable St. Gallen guidelines. No such difference was found among node-positive SD patients.

Table 2 Characteristics of node-negative high-risk patients by detection mode

Characteristic	Symptomatic ($n = 247$)	SD ($n = 351$)	<i>P</i> value
Median tumour size (mm)	15	12	0.000*
Tumour size >20 mm (%)	33	15	0.000
Tumour grade distribution (%)			0.003
Grade 1	1	3	
Grade 2	46	60	
Grade 3	45	32	
Unknown	9	5	
Tumour grade ≥ 2 (%)	90	92	0.46
Negative ER/PgR status (%)	20	15	0.11
Pattern of high risk (%) ^a			0.000
1) Tumour size >20 mm alone	7	3	
2) Tumour grade ≥ 2 alone	55	73	
3) Negative ER/PgR status alone	2	5	
1 + 2	18	9	
1 + 3	1	1	
2 + 3	10	8	
1 + 2 + 3	7	2	

* For the Mann–Whitney U test. All other *P* values are for the Pearson χ^2 test

^a Combination of characteristics that define a node-negative breast cancer patient at high risk according to guidelines from the 5th, 6th, and 7th St. Gallen International Conferences (depending on the date of diagnosis)

SD = Screen-detected; ER/PgR = Estrogen and/or progesterone receptor

Table 3 Characteristics of node-positive patients by detection mode

Characteristic	Symptomatic ($n = 259$)	SD ($n = 171$)	<i>P</i> value
Median tumour size (mm)	22	17.5	0.000*
Tumour size >20 mm (%)	53	30	0.000
Tumour grade distribution (%)			0.007
Grade 1	5	11	
Grade 2	31	40	
Grade 3	49	36	
Unknown	16	14	
Tumour grade ≥ 2 (%)	80	75	0.32
Negative ER/PgR status (%)	17	13	0.29
Median number of positive lymph nodes	3	2	0.028*

* For the Mann–Whitney U test. All other *P* values are for the Pearson χ^2 test

SD = Screen-detected; ER/PgR = Estrogen and/or progesterone receptor

Table 4 Proportion of node-negative high-risk patients and node-positive patients receiving adjuvant systemic therapy, by detection mode

Patients	Total patients		Total treated (%)			According to guidelines ^a (%)		
	Symptomatic	SD	Symptomatic	SD	<i>P</i> value	Symptomatic	SD	<i>P</i> value
Node-negative high-risk (<i>n</i> = 598)								
ER/PgR-positive	130	209	60	62	0.69	45	35	0.07
ER/PgR-negative	49	52	53	35	0.06	51	31	0.038
ER/PgR status unknown	68	90	63	63	0.99	38	32	0.43
Total	247	351	60	58	0.69*	45	34	0.011*
Node-positive (<i>n</i> = 430)								
ER/PgR-positive	164	112	73	76	0.61	63	71	0.16
ER/PgR-negative	43	22	70	68	0.90	70	68	0.90
ER/PgR status unknown	52	37	83	78	0.61	75	73	0.83
Total	259	171	75	75	0.97*	67	71	0.38*

* For the Mantel-Haenszel χ^2 test stratified by ER/PgR status. All other *P* values are for the Pearson χ^2 test

^a Treated according to guidelines from the 5th, 6th, and 7th St. Gallen International Conferences (depending on the date of diagnosis)

SD = Screen-detected; ER/PgR = Estrogen and/or progesterone receptor

For node-negative SD patients, the unadjusted OR of being treated according to the guidelines was 0.61 (95% CI, 0.44–0.86). With simultaneous adjustment for patient age, referral hospital, time period, ER/PgR status, tumour grade, and tumour size (upper row in Table 5), there was no difference whatsoever in the likelihood of SD cancers receiving the standard treatment. Sequential removal of covariates showed that tumour size was the strongest confounder. At the last step of the procedure, the removal of this variable decreased the OR from 0.79 to the unadjusted value of 0.61, which means that tumour size alone accounted for approximately 50% of the decrease in the crude odds of SD patients being treated according to the guidelines. The confounding effect of time period, tumour grade, and referral hospital was weaker. In particular, the effect of time period reflected the greater prevalence of SD patients in the second half of the study period (due to

increasing screening coverage) coupled with lower levels of adherence to the 1998 and 2001 St. Gallen guidelines compared with those released in 1995 (data not shown).

In the equivalent model for node-positive patients (data not shown), a term for the number of positive lymph nodes was also entered. Neither the detection mode nor other factors were significantly associated with receipt of adjuvant systemic therapy according to the guidelines. With simultaneous adjustment for all covariates, SD patients had an OR of 1.19 (95% CI, 0.75–1.87). After removal of covariates, the OR was 1.21 (95% CI, 0.79–1.85).

Discussion

Node-negative high-risk SD patients had a 40% decrease in the unadjusted OR of being treated according to the

Table 5 Odds ratio of node-negative, high-risk, screen-detected patients receiving adjuvant systemic therapy according to guidelines from the 5th, 6th, and 7th St. Gallen International Conferences (depending on the date of diagnosis)

Model	Variables in the model	<i>P</i> value*	Odds ratio ^a	95% confidence interval
1	All	–	0.99	0.67–1.46
2	Model 1 minus ER/PgR status	0.42	0.99	0.67–1.46
3	Model 2 minus patient age	0.16	0.94	0.64–1.38
4	Model 3 minus referral hospital	0.046	0.91	0.62–1.32
5	Model 4 minus tumour grade	0.006	0.86	0.60–1.24
6	Model 5 minus time period	0.001	0.79	0.55–1.14
7	Model 6 minus tumour size (detection mode alone)	0.000	0.61	0.44–0.86

* For the variable removed from the model

^a Odds ratios were estimated using binary logistic regression analysis (backward stepwise method). The variables were sequentially removed on the basis of the least significant contribution to the likelihood of the model. Node-negative high-risk patients with symptomatic breast cancer were the reference category

ER/PgR = Estrogen and/or progesterone receptor

guidelines from the 5th, 6th, and 7th St. Gallen Conferences, which was, however, entirely explained by known confounding factors. Approximately half of the decrease was accounted for by the smaller tumour size of SD cancers, while the confounding effect of time period, tumour grade, and referral hospital was more limited.

Once a patient was placed in the node-negative high-risk category, the guidelines assigned no role to tumour size in treatment decisions. In contrast, our data showed that increasing tumour size was associated with an increasing likelihood of patients receiving the standard adjuvant systemic therapy. Due to its broad definition (i.e., tumour size >20 mm and/or tumour grade ≥ 2 and/or negative ER/PgR status), the node-negative high-risk category of breast cancers encompassed a wide range of prognostic profiles [21]. As shown in Table 2, SD cancers amplified this heterogeneity. Their shift to lower tumour stage and grade meant that these patients were more likely to be placed in the high-risk category based on one feature only, and more often because of a histological grade 2 than a grade 3 or a size >20 mm. The lower likelihood of SD patients being treated according to the guidelines reflected the fact that, albeit nominally “at high risk”, they had a more favourable prognostic profile than their symptomatic counterparts. This is equivalent to saying that no evidence was found to suggest that physicians held a priori assumptions about the relative biological indolence of these tumours.

To some extent, this finding was expected. During the study period, allocation of patients with grade 2 tumours to the high-risk category was a controversial issue of the St. Gallen guidelines for node-negative patients [21], especially in view of observer variability of histological grading of breast cancer. In the study area, during the same period, a survival analysis confirmed the limited prognostic value of tumour grade as routinely reported [22]. In the present study, the effect of tumour grade on treatment decisions—albeit weaker than that of tumour size—indicated that grade 3 was considered a more reliable predictor of the risk of recurrence than grade 2.

The observed effect of the time period is consistent with this interpretation. We found that the 1998 and 2001 St. Gallen guidelines were less strictly adhered to than those released in 1995. In fact, the 1998 and 2001 Conferences approved the recommendation that the previous threshold for chemotherapy among node-negative cancers be lowered [21]. This increased the likelihood of patients in the present study not to receive the recommended therapy. In particular, although small numbers did not allow formal subgroup analyses, we found that two-thirds of all node-negative SD patients not treated according to the guidelines were accounted for by ER/PgR-positive patients receiving hormone therapy alone rather than chemo/hormone therapy as recommended by the 1998 and 2001 St. Gallen Conferences.

This latter finding deserves further comment. In the 1998 and 2001 guidelines, a low risk of relapse was mentioned as one of the conditions that “...might justify...” the use of hormone therapy alone [16, 17]. This concept was rapidly evolving and at the 2003 St. Gallen Conference, just after the time period of this study, endocrine therapy alone or combined chemo/hormone therapy were both considered to be adequate treatment options [23]. Using a restrictive definition of the standard treatment, i.e., the first-choice treatment during the time period studied, we were able to demonstrate that the subordinate treatment option was more often chosen for SD patients.

For the second subgroup of study patients, those with node-positive cancers, only a brief comment is needed. Even among these patients, detection by screening was associated with a favourable distribution by tumour size and grade. It is worthy of note that this supported the rationale for their inclusion into the study. The treatment decisions, however, were independent of all factors considered, including the detection mode. It clearly appears that the treating physicians considered node-positive SD cancers to be only formally preclinical.

Many problems arise when attempting to evaluate the use of chemo/hormone therapy in the community setting. First, information on the prognostic features needed for risk determination is often absent from routine medical records [19, 20], and further losses in completeness and quality of data may occur during the cancer registration process [24]. This is especially true for ER/PgR data. The cancer registries that participate in the Surveillance, Epidemiology, and End Results programme of the U.S. National Cancer Institute began collecting data on ER/PgR status of breast cancer in 1990, and only in 2001 did the proportion of cases with no recorded information decrease to less than 20% [25]. The result obtained for the present study, 24% of cases in the final analysis, is acceptable. Moreover, a data quality check comparing SD cancers and symptomatic cancers (see the ‘Data analysis’ section) showed no selective loss of data.

Second, non-surgical treatments are often provided in outpatient and day-hospital settings, where case records are less accessible and less complete than in inpatient settings [26]. Moreover, information on nonclinical factors involved in treatment decision—such as patient preference—is usually not available for retrospective studies [27]. In the present study, missing information accounted for two large subgroups of ineligible patients, i.e., all patients living in a health district where access to treatment data was incomplete (about 10% of total registered cases), and patients who were classified as lost to post-surgical follow-up. However, we believe that this did not substantially affect results as the first subgroup was an unselected population and the second was almost equally distributed between SD and symptomatic cancers.

Partial loss of treatment data might also have occurred in the subgroup of eligible patients. According to the data collected, the total rate of adjuvant systemic therapy (symptomatic and SD patients combined) was 59% for node-negative patients and 75% for node-positive patients (data not shown). A high-quality study from community settings in the United States has reported rates of 65 and 88% [26]. Using these results as standards for unadjusted comparisons, however, is unwarranted. Moreover, the present study was designed to assess treatment differences and not total treatment rates. The following considerations suggest that the comparison of SD with symptomatic patients was unlikely to be seriously biased: (1) the quality of information for risk determination was the same; (2) screening and clinical mammography services in the study area are provided by the same institutions, and the provision of chemotherapy services is centralized in public hospitals; (3) it is implausible that clinical records in each place of treatment are less accurate for SD patients; and (4) a term for the referral hospital was included in multivariate analysis to account for potential differences in patient flow to medical oncology services.

In conclusion, the present study showed that some of the major weaknesses found [21] in the 1995, 1998, and 2001 St. Gallen guidelines were more pronounced for the treatment of SD cancers. The results can be summarized as follows: (1) SD cancers amplified the prognostic heterogeneity of node-negative patients in the high-risk category of the St. Gallen classification; (2) SD patients in this category were less likely to be treated according to the guidelines than symptomatic patients, which was largely explained by their lower risk profile; and (3) there was no evidence that physicians held a priori assumptions about the relative biological indolence of SD cancers.

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