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ORIGINAL ARTICLES

REVIEW ARTICLE

CASE REPORTS

Professor Krzysztof Krzemieniecki Award for the best case report accepted for publication

Case Report Contest Policies

This policy defines the scope, requirements and regulations regarding **The Krzysztof Krzemieniecki Award** for the best case report published in "Oncology in Clinical Practice" (OCP) Sixth Edition.

1. The aim of the contest is to encourage submission of quality case reports related to oncological practice and to promote them in the scientific deliberations.
2. All respective manuscripts submitted to OCP between June 1st, 2021 and May 31st, 2022 and accepted for publication will qualify.
3. Manuscripts should be prepared in line with Authors' guidelines and should be submitted only through the manuscript system available at Journal's website: https://journals.viamedica.pl/oncology_in_clinical_practice
4. All submitted manuscripts will be evaluated during the peer review process and authors will be informed about their qualification for publication in OCP. Accepted papers will be evaluated by the Contest Committee based upon fulfillment of the Contest criteria as well as practical significance, originality, applicability and addressing of current/critical concerns.
5. The first author of the winning paper will be eligible for a prize of gross 1000,00 Euro gross (one thousand euro).
6. Results will be announced during the XXV National Congress of The Polish Society of Clinical Oncology and subsequently at the Journal website.
7. Winner will be notified via email.
8. Contest Committee may exclude a paper from participation in case of potential conflict of interest or ask submitting author for adequate clarifications.
9. The Sponsor at any stage and in any respect, will not participate in the evaluation of entries and selection of a winning paper.
10. The award amount shall be paid based on the copyright transfer agreement to the paper.
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ORIGINAL ARTICLE

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Prophylactic hyperthermic intraperitoneal chemotherapy in gastric cancer management: short- and long-term outcomes of a prospective randomized study

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ABSTRACT

Introduction. Assessment of toxicity and long-term results of hyperthermic intraperitoneal chemotherapy (HIPEC) treatment administered to patients with resectable serosa-invasive gastric cancers.

Material and methods. The study was carried out in 2008–2016 and is based on the results of the treatment of 154 gastric cancer patients (stage IIB–IIIC, III–IV Borrmann type) who were randomly assigned to two groups. 76 patients underwent HIPEC combined with radical gastrectomy (HIPEC group) and 78 patients underwent radical gastrectomy without HIPEC (control group). HIPEC was administered after alimentary tract reconstruction and wound closure and comprised 5–6 L of Ringer's solution (cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2) infused at an inflow temperature of 42°C for 1 hour.

Results. Although the total number of complications was higher in the HIPEC group than in the control group the difference was statistically insignificant — 20 (26.3%) and 12 (15.3%), respectively (p = 0.141). Surgery-related complications in the HIPEC and control groups were observed in 9 and 5 cases, respectively (p = 0.372). Non-surgical complications were recorded in 11 and 7 cases, respectively (p = 0.435). Overall, the proposed HIPEC regimen administered in combination with radical surgery demonstrated satisfactory patient tolerability. The frequency of grade III toxic reactions according to CTCAE *version* 5.0 was 9.2%, no grade IV–V toxicities were registered at that. These satisfactory short-term results were followed up with fairly good long-term treatment outcomes. There was an increase in 5-year progression-free survival (42.1 ± 6.3% *vs.* 16.3 ± 5.5%, p < 0.001) and in dissemination-free survival (45.2 ± 6.3% *vs.* 19.4 ± 5.9%, p = 0.001) in the HIPEC group *vs.* the control group with a trend toward improving cancer-specific survival (CSS) in the HIPEC-treated patients [45.1.0 ± 6.4% *vs.* 27.0 ± 6.7% (p = 0.050)].

Conclusions. While substantially improving long-term GC therapeutic effect, the proposed HIPEC regimen using cisplatin 50 mg/m^2 in combination with doxorubicin 50 mg/m^2 made it possible to minimize complications (frequency of 26.3%) and toxic reactions [the frequency of grade III toxic reactions was 9.2% (CTCAE, *version* 5.0)].

Key words: serosa-invasive gastric cancer, hyperthermic intraperitoneal chemotherapy, toxicity, randomized trial

Oncol Clin Pract 2021; 17, 5: 187–193

Introduction

The present report focuses on analyzing and systemizing short- and longer-term outcomes of managing radical surgery/hyperthermic intraperitoneal chemotherapy (HIPEC) treated patients in the context of observed post-HIPEC toxicity in patients. Being a follow-up to our previous publications [1, 2] that dealt with long-term

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preventive efficacy assessment of HIPEC with regard to the peritoneal recurrence of gastric carcinoma in patients, this report is likewise based on the outcomes of our randomized study undertaken at the National Cancer Center of Belarus in 2008–2016. The present report incorporates the study's underlying assumptions, principles and methodology and includes its main statistical data and descriptive information for the sake of ensuring coherence in the presentation of research results.

The trial was approved by the Ethics Committee of the N.N. Alexandrov National Center, and a written informed consent was obtained from all the patients.

Material and methods

Patients

As we reported previously [2], the study involved patients with histologically confirmed gastric cancer, aged 18–70, T4a-bN0-3M0, stage IIB–IIIC, with preoperative ECOG status of 0–I, without esophagus involvement, who underwent a potentially curative operation (i.e. R0 resection). Resectable serosa-invasive gastric cancer patients were included in the study only after intraoperatively obtaining morphological confirmation of serosal invasion (pT4) by employing a frozen section procedure. Borrmann type III–IV was used as an inclusion criterion. Resectability was established according to the results of a pre-operative CT and ultrasonographic examination.

Surgical treatment consisted of total or partial (distal subtotal resection) gastrectomy with free margins (R0 resection) and D2 lymph node dissection, in case of necessity supplemented by liver, distal pancreatic or transverse colon resections.

HIPEC regimen

HIPEC was performed after gastrectomy/alimentary tract reconstruction and wound closure. One inflow catheter (30F) was positioned beneath the left hemidiaphragm. Three outflow catheters (32F) were placed in both the true and false pelvises in the subhepatic area. Temperature probes were placed on the inflow and outflow catheter tips. HIPEC was administered for one hour with an automatic HIPEC device. Perfusate used was Ringer's solution (5–6 L) mixed with cisplatin 50 mg/m^2 + doxorubicin 5 0 mg/m^2 warmed to an inflow temperature of 42°C. Since the study was launched in 2008, i.e. prior to accepting perioperative chemotherapy as a standard requirement in GC management, none of the patients in the study was administered perioperative chemotherapy.

The severity of HIPEC-related side effects was measured using the CTCAE grading scale, v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_ quick_reference_5x7.pdf).

As was previously reported [2], progression-free survival (PFS) was the primary endpoint of the study. PFS was measured from the date of random assignment to the date of gastric cancer progression. Secondary endpoints included dissemination-free survival (DFS), measured from the date of random assignment to the date of gastric cancer progression with metachronous peritoneal metastases, cancer-specific survival (CSS), measured from the date of random assignment to the date of death from the same cancer, and overall survival (OS), measured from the date of random assignment to the date of death from any cause. All same cancer recurrences (metachronous peritoneal metastases, distant metastases) and deaths from the same cancer were accounted for as events.

Statistical analysis

Descriptive analysis variables were expressed as mean ± standard deviation (SD) or counts and percentages [n (%)], as appropriate. Also used for groups' comparison were t-test, Chi-square test, and Fisher's exact test, if assumptions of Chi-square test were violated. The survival rate was assessed applying the Kaplan-Meier estimator. Multivariate Cox model was used to determine PFS risk factors. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using an exponential transformation of the respective parameters of the models.

Statistical analysis of the data was performed using the R version 3.1.1 statistical software (GPL license) [3].

Results

Patient characteristics

As we mentioned previously [2], between 2008 and 2016 a total of 478 patients gave their consent to participate in the trial. However, as the trial progressed, 27 patients withdrew their consent to participate, 281 patients were excluded as not intraoperatively confirmed to have serosal invasion (pT2N0-3M0; pT3N0-3M0), and 16 patients were excluded due to the presence of co-morbidities that led to the reduction of the volume of lymph node dissection to D1. As a result, the trial included 154 patients with gastric cancer [stage IIB–IIIC (T4a-bN0-3M0), III–IV Borrmann type], without esophagus involvement, who underwent a potentially curative operation (i.e. R0 resection), and who were randomized after intraoperative

Table 1. Patient characteristics

Variable	HIPEC group, n = 68 (%)	Control group, n = 55 (%)	p
Gender (male/female)	44 (64.7)/ /24 (35.3)	34 (61.8)/ /21 (38.2)	0.74
Age [yrs], mean ± SD	56 ± 8	56 ± 9	0.75
pT			0.46
pT4a	55 (80.9)	48 (87.3)	
pT4b	13 (19.1)	7 (12.7)	
pN			0.76
pN0	23 (33.8)	14 (25.5)	
pN1	8 (11.8)	6 (10.9)	
pN2	15 (22.1)	14 (25.5)	
pN3	22 (32.4)	21 (38.2)	
G			0.14
GI	6 (8.8)	4 (7.3)	
GII	17 (25.0)	9 (16.4)	
GIII	39 (57.4)	29 (52.7)	
GIV	6 (8.8)	13 (23.6)	

SD — standard deviation

morphological confirmation of serosal invasion (pT4) based on frozen section procedure. The evaluation of toxicities and surgical complications was based on the results of treating the aforesaid 154 patients including 76 patients in the HIPEC group (male/female — 50/26) and 78 patients in the control group (male/female — 45/33). The assessment of long-term treatment results included 123 patients whose data were available for analysis. Excluded from this analysis as not meeting the study inclusion criteria were 8 patients from the HIPEC group (R1 resection — 2 patients, unconfirmed gastric cancer — 1 patient, Borrmann type I–II — 5 patients) and 23 patients from the control group (R1 resection — 2 patients, unconfirmed gastric cancer — 1 patient, Borrmann type I–II — 14 patients, refused to participate in the study — 3 patients, early withdrawal, no data available — 3 patients). The two groups were well balanced (Tab. 1).

Complications

Complications were observed in 13 patients in the HIPEC group and in 11 patients in the control group with 2 or more complications diagnosed in 5 patients in the HIPEC group and in 1 patient in the control group. Although the total number of complications in the HIPEC group was higher than in the control group it was statistically insignificant — 20 (26.3%) and 12 (15.3%), respectively (p = 0.141). Surgery-related complications in the HIPEC and control groups were observed in 9 and 5 cases, respectively (p = 0.372) (Tab. 2), non-surgical complications — in 11 and 7 cases, respectively (p = 0.435) (Tab. 3).

Hematological toxicity was the most frequently registered side-effect reaction. However, no grade IV–V toxic reactions were observed, while grade III toxicities were basically of hematological origin and did not exceed

Table 2. Postoperative morbidity (surgical complications)

Type of complications	n (%)	CTCAE v 5.0 grade
HIPEC group		
Postoperative pancreatitis	4 (44.4%)	II
Pancreatic fistula	1 (11.1%)	II
Volvulus of ileal loops, serosal peritonitis	1 (11.1%)	IV
Mesothrombosis	1 (11.1%)	V
Esophagojejunal anastomotic leak	2 (22.3%)	V
Total:	9 (100%)	
Control group		
Wound infection	2 (40.0%)	II
Postoperative pancreatitis	2 (40.0%)	II
Left liver lobe necrosis, paralytic intestinal obstruction	1 (20%)	IV
Total:	5 (100%)	

HIPEC — hyperthermic intraperitoneal chemotherapy

Table 3. Postoperative morbidity (non-surgical complications)

Type of complications	n (%)	CTCAE v 5.0 grade
HIPEC group		
Enterocolitis	1 (9.1%)	I
Fever of unclear genesis	2 (18.1%)	I
Pneumonia	5 (45.5%)	II
Pleural effusion	1 (9.1%)	II
Thrombophlebitis of subcutaneous veins	1 (9.1%)	II
Acute kidney failure	1 (9.1%)	II
Total:	11 (100%)	
Control group		
Pneumonia	4 (57.1%)	II
Myocardial infarction	1 (14.3%)	II
Acute ischemic stroke	1 (14.3%)	V
Acute gastroenteritis of allergic origin	1 (14.3%)	II
Total:	7 (100%)	

HIPEC — hyperthermic intraperitoneal chemotherapy

Table 4. Toxicity profile of HIPEC-treated patients (CTCAE, v 5.0)

Event	Degree of toxicity, n, %				
	I	II	III	IV	V
Gastrointestinal toxicity					
Nausea	18 (23.7%)	4 (5.3%)	–	–	–
Vomiting	4 (5.3%)	3 (3.9%)	–	–	–
Diarrhea	4 (5.3%)	2 (2.6%)	–	–	–
Hematological toxicity					
Anemia	20 (26.3%)	9 (11.8%)	1 (1.3%)	–	–
Lymphocyte count decreased	35 (46.1%)	19 (25%)	6 (7.9%)	–	–
Neutrophil count decreased	1 (1.3%)	–	–	–	–
Thrombocytopenia	–	–	–	–	–
Metabolic toxicity					
Aspartate aminotransferase	31 (40.8%)	3 (3.9%)	–	–	–
Alanine aminotransferase	24 (31.6%)	4 (5.3%)	–	–	–
Blood bilirubin increased	2 (2.6%)	3 (3.9%)	–	–	–
Creatinine increased	2 (2.6%)	3 (3.9%)	–	–	–
Constitutional symptoms	2 (2.6%)	2 (2.6%)	–	–	–

9.2% (7 patients). That puts our study at an advantage compared with earlier reported trials [7–10] (Tab. 4).

Another positive outcome of the proposed HIPEC regimen was survival rate improvements compared with surgery-only GC treatment. There was a statistically significant increase in 5-year progression-free (42.1 ± 6.3% *vs.* 16.3 ± 5.5%, $p < 0.001$) and dissemination-free (45.2 ± 6.3% *vs.* 19.4 ± 5.9%, $p = 0.001$) survivals in the HIPEC group with a trend toward improving cancer-specific survival (CSS) in the HIPEC-treated patients [45.1.0 ± 6.4% *vs.* 27.0 ± 6.7% ($p = 0.050$)] (Fig. 1–3).

The effect of the proposed combined HIPEC/surgery treatment on prognosticating GC progression risks was measured by means of a regression analysis based on the Cox proportional hazards model. Covariates used in the model included HIPEC proper, the state of regional lymph node (pN0, pN1-2, pN3), and performed surgical procedure. The model did not include universally known factors of adverse prognostication used as inclusion criteria in the present study (macroscopic growth form – stage III–IV in the Bormann classification, serosal invasion by tumor or tumor invasion of adjacent structures – pT4a–b, and D2 lymph node dissection) (Tab. 5).

As we reported earlier [2] our multivariate Cox model analysis showed an increased risk of disease progression in (a) cases of regional lymph node metastases; (b) cases requiring gastrectomy or combined gastrectomy; and (c) the control group. The analysis manifestly demonstrated a high risk of GC progression in the absence of HIPEC treatment and highlighted

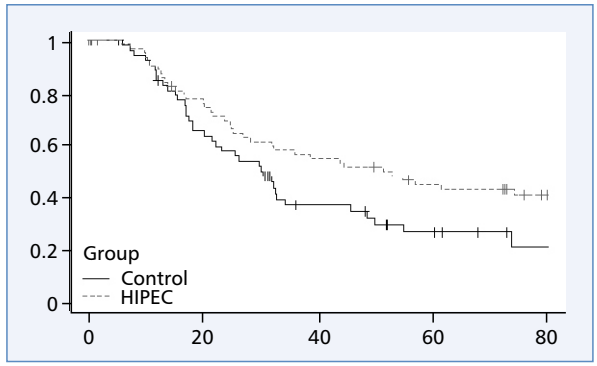

Figure 1. Cancer-specific survival in the HIPEC and control groups; HIPEC — hyperthermic intraperitoneal chemotherapy

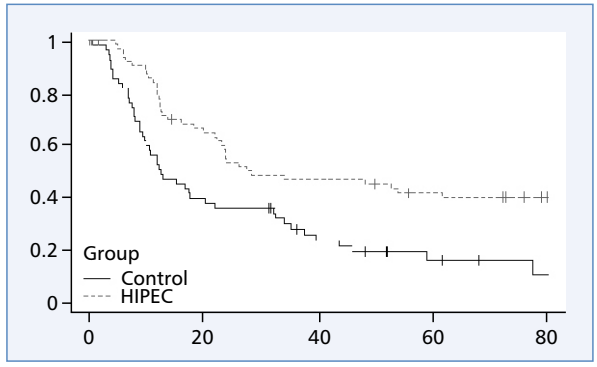

Figure 2. Progression-free survival in the HIPEC and control groups; HIPEC — hyperthermic intraperitoneal chemotherapy

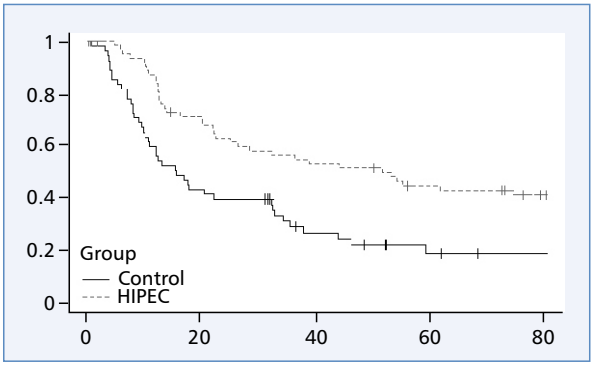

Figure 3. Dissemination-free survival in the HIPEC and control groups; HIPEC — hyperthermic intraperitoneal chemotherapy

Table 5. Factors associated with gastric cancer progression (Cox model)

Variables	β	HR (95% CI)	p
pN1–2 *vs.* pN0	0.88	2.4 (1.3–4.6)	0.008
pN3 *vs.* pN0	1.51	4.5 (2.4–8.6)	< 0.001
Gastrectomy + combined gastrectomy *vs.* subtotal gastric resection	0.63	1.9 (1.1–3.1)	0.013
Surgery *vs.* surgery + HIPEC	0.7	2.0 (1.3–3.0)	0.003

HR — hazard ratio; CI — confidence interval; HIPEC — hyperthermic intraperitoneal chemotherapy

the importance of this adjuvant treatment mode in the management of radically operated GC patients.

Discussion

The data presented above are consistent with the findings of some authors [4–6], who also observed no difference in the number of postoperative complications between the HIPEC/surgery group of patients and the surgery-only group of patients. For example, Kim and Bae (2001) [4] reported that the number of postoperative complications in the patients of the HIPEC and control groups was 36.5% and 33.3%, respectively. In our study these figures were 25.6% and 15.4%, respectively. Also, compared with similar published studies [7–10], a noteworthy outcome of the proposed HIPEC regimen was the absence of grade IV–V toxic reactions.

Chemo-tolerability in the overall evaluation of the efficacy of any chemotherapy regimen is a no less important factor ensuring adequate quality of life than improvements in long-term GC treatment outcomes [11].

Since the first trials of HIPEC prophylactic treatment of peritoneal recurrence after GC surgery were initiated in the late 1980s — the early 1990s [12–15], researchers have been faced with a dual task of assessing and improving HIPEC prophylactic efficacy, and simultaneously, of striving to maintain toxicities at a tolerable level. Both of these tasks have been tackled with a varying degree of success by experimenting with the choice, dosage and delivery of chemotherapy drugs.

According to some researchers, most of the cases of HIPEC-related nephro- and hepatotoxicity were caused by cisplatin [8, 16, 17]. For example, Farma et al. (2005) [8] observed hematological toxicity in 27.8% of patients and impaired kidney function in 16.7% of patients at a cisplatin dosage of 150–300 mg/m^2. Kusamura et al. (2006) [17] showed that the administration of cisplatin at a dose of ≥ 240 mg/m^2 was associated with a high risk of grade III–IV complications according to the WHO criteria. Juan et al. (2018) [10] reported that the platinum-based HIPEC regimen was fraught with a heightened risk of kidney function impairment — RR 3.04 (95% CJ 1.71–5.39), p < 0.001. According to some reports, the use of cisplatin in combination with mitomycin C caused hematological toxicity in 2.5–5.3% of cases [7, 9]. In particular, it was reported that the use of only cisplatin at 1 mg/kg or of cisplatin at 0.5 mg/kg in combination with mitomycin C at 0.7 mg/kg resulted in grade III–IV hematological toxicity in 4.6% of cases and nephrotoxicity — in 1.3% of cases [7]. When using a combination of cisplatin at 25 mg/m^2/L + mitomycin C at 3.3. mg/m^2/L or cisplatin at 43 mg/L + doxorubicin 15.25 mg/L, Kusamura et al. (2007) [9] observed grade III–IV hematological toxicity in 5.3% of cases and nephrotoxicity in 5.7% of cases.

Proceeding from this information, we decreased the dosage of cisplatin to 50 mg/m^2. We also took note of the research data emphasizing the need for a combined application of cisplatin with other chemotherapy drugs to ensure long-term GC treatment improvements compared with treatment outcomes based on cisplatin-only intraperitoneal chemotherapy [5, 18–20]. Analyzing three cisplatin-only HIPEC efficacy trials [18–20], Feingold et al. noted in their meta-analysis (2017) [5] that the RR of the 5-year mortality was 0.79 (95% CI 0.60–1.04; p = 0.09) with 2 of these studies (including one conducted in Europe [18]) failing to produce any statistically significant reduction in 5-year mortality.

Taking into account the data on the ways of improving HIPEC efficacy available prior to the start of our trial we opted in favor of combining cisplatin with doxorubicin as one of the most effective cytostatic drugs in GC treatment, yet proven safe in intraperitoneal application as was reported by Sugarbaker et al. (2005) [21]. Our choice of cisplatin/doxorubicin combination was also prompted by their multidirectional cancer-killing potential thereby producing a synergic cancericidal effect. Proceeding from the published research data about the relatively low level of doxorubicin-related toxicities [21],

we raised its dosage to 50 mg/m^2 to add to the anti-cancer potential of cisplatin whose dosage was lowered in our study on account of its comparatively high toxicity.

Despite the increase in the doxorubicin dosage to 50 mg/m^2 exceeding that in similar studies, for example, a doxorubicin dose escalation study by Sugarbaker [22], no clinical manifestation of peritoneal adhesions was observed during the follow-up monitoring period. Nor were there any pronounced adhesion processes or intestinal fibrosis registered during second-look laparoscopy. This outcome could possibly be attributed to a larger than usual volume of perfusate used in our study (5–6 L).

Viewed overall, the above discussed dosage combination of cisplatin and doxorubicin proved to be effective both in terms of ensuring adequate patient tolerability and achieving good prophylactic efficacy outcomes of the proposed HIPEC regimen.

A serious downside of the present study was the absence of systemic chemotherapy in the management of radically operated GC patients that is accounted for by the fact that at the time of launching the trial in 2008 there was no universal standard of applying perioperative chemotherapy in the GC treatment.

As if to highlight this drawback, the results of our study amply showed a need for supplementing adjuvant HIPEC with systemic chemotherapy in view of an increased risk of distant metastases [β = 0.2; RR 7.5 (95% CI 2.2–25) $p < 0.001$] against the backdrop of a reduced risk of developing metachronous peritoneal metastases [β = –1.60; RR 0.2 (95% CI 0.11–0.37), $p < 0.001$] [2]. In our subsequent study combining HIPEC (cisplatin 50 mg/m^2 and doxorubicin 50 mg/m^2) and 8 cycles of systemic chemotherapy (capecitabine + oxaliplatin or tegafur + oxaliplatin) we managed to improve long-term treatment outcomes by reducing the frequency and cumulative incidence of both metachronous peritoneal and distant metastases while achieving an adequate patient tolerance to the combined application of HIPEC and adjuvant systemic chemotherapy [23, 24].

Furthermore, the low toxicity levels of the proposed HIPEC regimen (cisplatin 50 mg/m^2 and doxorubicin 50 mg/m^2) demonstrated in our study give grounds to hypothesize the possibility of combining this HIPEC regimen not only with postoperative chemotherapy but also with chemotherapy administered perioperatively. Such a treatment strategy seems to be especially promising for managing patients exposed to a high risk of developing peritoneal dissemination, for example, patients with grade pT4b cancer. Obviously, further studies are needed to explore this possibility.

Conclusions

While substantially improving long-term GC therapeutic effect, the proposed HIPEC regimen using cisplatin 50 mg/m^2 in combination with doxorubicin 50 mg/m^2 made it possible to achieve satisfactory patient tolerability results both in terms of complications (frequency of 26.3%) and toxicity (the frequency of grade I–III toxic reactions was 9.2% according to CTCAE, *version* 5.0).

However, it is obvious that despite a growing number of positive reports on using adjuvant HIPEC for the treatment of gastric cancer associated with a high risk of implantation metastasis it is in many cases a 'hit-or-miss' process which means that we are still a long way off from developing definitive evidence-based recommendations and guidelines on the most effective HIPEC procedural techniques and combinations of chemotherapy agents to offer to clinicians, and likewise, from proposing optimal systemic chemotherapy regimens to be used in combination with HIPEC, a goal that can only be attained by conducting further studies in this field of research.

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No funding was received.

Conflict of interest

The authors have declared no conflicts of interest.

Ethics approval

The trial was approved by the Ethics Committee of the N.N. Alexandrov National Cancer Center.

Consent to participate

Written informed consent was obtained from all patients before trial entry.

Consent to publish

Not applicable.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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VIA MEDICA

ORIGINAL ARTICLE

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The effect of education training intervention on the caregiver burden among mothers of children with leukemia: a quasi-experimental study

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ABSTRACT

Introduction. Leukemia is a broad term that refers to a group of malignant diseases of the bone marrow and lymphatic system. Caregiver burden is one of the issues that are faced by primary caregivers, and this role is played by mothers in most cases. In addition to these problems, mothers experience frustration in performing tasks, isolation and failure due to inadequate education about the disease and inadequate information support. The aim of the present study was to determine the effect of education on the caregiver burden (CB) among mothers of children with leukemia.

Material and methods. The present quasi-experimental study was performed on mothers of children with leukemia in the Hematology Ward of Ali ibn Abi Talib Hospital of Zahedan in 2019. Convenience sampling was used to select eligible mothers. At the baseline, the control group was selected according to the inclusion criteria (this method was to prevent the effect of the intervention on the control group). Then, a questionnaire including demographic information, and caregiver burden inventory (CBI) were completed in two stages: pre-test and post-test. To this end, after completing the questionnaire, the first training session was held in the hematology department individually for 30 to 45 minutes with a specific content. Also, after completing three training sessions, phone follow-up was performed weekly for 4 weeks to ensure that the intervention was implemented. The questionnaires were redistributed and recompleted by intervention and control groups again four weeks after the intervention.

Results. The mean pre-intervention CB score in the intervention and control groups was 19.97 ± 5.25 and 18.97 ± 10.03, respectively. The mean post-intervention CB score was also 17.17 ± 4.78 and 19.18 ± 9.93, respectively. Intervention significantly reduced CB score in the intervention group ($p < 0.001$).

Conclusions. The findings showed that training was effective in reducing the CB score among mothers of children with leukemia. Therefore, it is recommended to use training as a non-pharmacological and appropriate method in reducing CB among mothers of children with leukemia.

Key words: educational intervention; caregiver burden; leukemia; mothers

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Introduction

Leukemia is the most common and well-known childhood cancer worldwide, and also the third leading cause of death in children aged 1 to 4 years [1]. In 2016, out of every 380 children aged under 15 years, 10 were diagnosed with cancer [2]. A total of 4% of children aged under 5 years and 13% of children aged 5 to 15 years died of cancer in Iran in 2010; while the youth (age less than 15 years) makes up 25% of the country's population [3]. Cancer is a disease that seriously undermines the physical and mental health of the patient and family members [4]. Caregiver burden (CB) is one of the issues facing primary caregivers, mainly moth-

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ers. Caregivers are people who accompany the patient in the treatment process and help him/her to adapt with the disease [5]. These caregivers not only play an important role in the physical care dimension such as nutrition, personal hygiene, movement and mobility, but also provide emotional and social support to the patient in the psychological dimension [6]. Therefore, while caring for patients with chronic diseases such as cancer, both the patient and his/her primary caregivers are exposed to a variety of physical and psychological crises, and these caregivers may feel a heavy burden of responsibility because they have to play an important role in supporting the patient. In this regard, caregivers need more social support [7]. For this reason, paying attention to caregivers as part of their disease is a top priority. Numerous studies have emphasized that cancer challenges caregivers by affecting various aspects of their lives and affects their quality of life [8]. In the meantime, mothers play a very prominent role because in addition to providing physical care alone in many cases, they suffer from psychological consequences and subsequent stress, anxiety, and fatigue due to the condition of the sick child, worries about the future of the disease, and the consequences of the disease. Studies on families of cancer children showed that when a child becomes ill, the mother becomes more involved in care and treatment process than the father, and the father tends to do other things and attempts to ensure the peace of other family members, which in turn causes mothers to experience a lot of change in their life. Moreover, mothers lose their job and social position and work few hours because of caring for the child [9]. In a study of quality of life of parents of children with leukemia and related factors, Khanjari et al. [10] found that the quality of life of mothers of children with leukemia is very inadequate and it is necessary to educate families, especially caregivers in the field of child care and know how to adapt to improve the living conditions of caregivers. With regard to psychological problems of mothers of children with leukemia, studies have shown that caregivers experience different problems in different communities [11]. Studies show that mothers of children with leukemia admitted to the oncology wards experience more CB than other caregivers due to their low chance of recovery and high dependence on caregivers in daily activities, worsening of the patient's conditions as the disease progresses, and treatment non-response [12]. While providing care to cancer patients, caregivers are themselves exposed to a variety of stressful situations, which is called caregiver burden (CB) in nursing resources [13]. CB refers to the stress that a caregiver feels as a result of caring for the patient and has physical, psychological and social dimensions. Moreover, increasing CB levels will lead to several consequences such as inadequate patient care, patient abandonment, and disruption of family and social relationships [14]. Studies on quality of life of cancer patients' family have shown that cancer has significant effects on the physical, psychological, social and economic dimensions of the patient's family [15]. The family has also been introduced as the best source of care for patients with leukemia. Unfortunately, there are poor support services for caregivers in Iran [16]. Considering the limited role of mothers in the family and doing chores, they pay less attention to their health in most cases, now if, in addition to the relevant chores, they play the role of the main caregiver of a sick child, they will spend more time dealing with the above matters, and in practice, these issues lead to CB in the long run. For this reason, it is necessary to consider both variables according to the fundamental role of mothers in the family. Therefore, determining the CB level and then planning to reduce it and increase support for the family and caregivers of cancer patients can play an important role in improvement of symptoms. Despite the high prevalence of cancer and the potential risk of CB in caregivers, physicians have paid less attention to this issue in Iran [17]. Safaeian et al. (2016) found that more than half of caregivers of cancer patients experience severe and very severe CB levels. They also confirmed that it seems necessary to evaluate primary caregivers by members of the treatment team and develop family-centered rehabilitation programs [18]. Therefore, it is necessary for mothers to have a good mood in order to be able to adequately adapt to the disease. One of the effective factors helping children adapt with chronic diseases such as leukemia is the role of their mothers who are their main supporter during treatment programs and play the main role in promoting the quality of health and adaptation to the disease. This role is affected by the patient's problems and to provide care along the care path is different. Therefore, it is necessary to teach mothers of these patients some appropriate solutions to cope with the disease. The aim of the present study was to investigate the education training intervention on caregiver burden among mothers of children with leukemia.

Material and methods

Design

This quasi-experimental pre-test-post-test study was performed on 90 mothers of children with leukemia hospitalized in Ali ibn Abi Talib Hospital of Zahedan located in southeastern Iran from February 10, 2019 to March 1, 2020. Participants were selected from among eligible mothers of hospitalized children with leukemia using convenience sampling method. The sample size was determined 37 people in each group using the results of the previous study.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(d)^2} = ٣٦/٥٢$$

$$Z_{1-\frac{\alpha}{2}} = ١/٩٦ \quad S_1 - ٣/٦٨ \quad Z_{1-\beta} = ٤/٢٢ \quad d = ٣$$

Data collection

After the research project was approved by the Ethics Committee and coordination was made with the management of hospital, the researchers referred to the head nurse of the pediatric ward. First, after getting acquainted with the children and mothers and gaining their informed consent, the researchers explained the purpose and method of the intervention to them. Also, sufficient explanations were given to them regarding the safety of participating in this study. The mothers were assured that their personal information would be kept confidential and that they could withdraw from the study at any time. At the baseline, the control group was selected according to the inclusion criteria (this method was used to prevent the effect of the intervention on individuals in the control group). Demographic information questionnaire and caregiver burden inventory (CBI) were completed in two stages, namely pre-test and post-test. Then the samples of the intervention group were selected. To this end, after filling out the questionnaires, the first training session covering a specific content was held in the hematology department for 30 to 45 minutes with each individual. The second and third training sessions were held in the same way one week later. After completing three training sessions, phone follow-up was performed weekly for 4 consecutive weeks to perform the provided trainings. Questionnaires were redistributed and recompleted by the intervention and control groups at the end of the intervention. In order to observe the ethical principles, the control group only received the routine ward care, and the training booklet was given to this group after the intervention.

Instruments

Data collection instruments include a questionnaire consists of two sections. The first section includes demographic characteristics of mothers (age, mother's education level, mother's employment status, number of children, presence of disease symptoms in the mother, child's sex, birth rank of the child). The second section includes the standard caregiver burden inventory (CBI). CBI was developed to assess the perceived burden in caregivers [18]. CBI consists of 24 items and the participant must determine how much he/she experiences each situation on a five-point Likert scale. This questionnaire measures CB in following five dimensions: Time-dependent burden (phrases 1–5): This subscale indicates the time constraint created for the caregiver following the addition of the care tasks to his or her previous tasks. Developmental burden (phrases 6–10): This subscale examines whether the caregiver feels that he or she is lagging behind less than his or her peers due to caring for the patient. Physical burden (phrases 11–14): This subscale describes the caregiver's feelings about threats or physical harm. Social burden (phrases 15–19): This subscale measures role conflict in the caregiver. Emotional burden (phrases 20–24): This subscale measures the negative feelings of the caregiver towards the person caring for him/her. The possible score range is 0 to 120 and higher scores indicate the higher negative effect of patient care on various aspects of caregiver's life. Cronbach's alpha coefficient of each suable and the whole questionnaire has been reported 0.68–0.78 and 0.78, respectively. Cronbach's alpha coefficient of the Persian version of this questionnaire has been reported 0.90.

Ethical considerations

The present study has been approved by the Ethics Committee of Zahedan University of Medical Sciences with the ethics code: IR.ZAUMS.REC.1398.340. Written and oral consent was received from all participants in the study. Participants were assured that their information will remain confidential.

Data analysis

Statistical analysis was carried out using SPSS ver. 21. To describe individual characteristics, descriptive statistics were used to determine central indicators and dispersion such as minimum, maximum, range of changes, mean, standard deviation, percentage and frequency. Paired t-test was used to compare the mean in each group before and after intervention. Independent t-test was also used to compare the mean of the two groups. Chi-square test was used to compare the frequency of qualitative variables of the two groups. Finally, analysis of covariance (ANCOVA) was used to determine the effectiveness of the intervention by simultaneously controlling some confounding variables. P-value 0.05 was considered as the significance level. Shapiro-Wilk test was used to test the normality of the distribution of observations.

Results

Based on the findings, the mean and standard deviation of children's age in the intervention and control groups was 9.61 ± 2.84 and 9.65 ± 2.28 years, respectively. The duration of cancer in the intervention and control groups was 2.10 ± 1.69 and 2.50 ± 1.85 years,

Table 1. Content of training sessions in reducing caregiver burden

First session	Definition of cancer, symptoms of complications, educational interventions	30–45 minutes
Second session	Reviewing the content of previous session, crisis management in cancer, spiritual methods of controlling stress and anxiety based on religious teachings	30–45 minutes
Third session	Reviewing the contents of previous sessions, solutions to control fatigue, distraction and energy conservation and relaxation strategies and teaching adequate sleep and rest methods	30–45 minutes

Table 2. Comparison of mean and standard deviation of CB score among mothers of children with leukemia in intervention and control groups before and after training

	Before educational intervention	After educational intervention	Changes in mean value	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
Intervention	70.62 ± 13.75	55.97 ± 7.16	14.65 ± 6.59	0.001
Control	71.28 ± 12.71	76.75 ± 13.93	5.47 ± 1.22	0.70

SD — standard deviation

respectively. There was no significant difference between the groups in terms of demographic and clinical symptoms. The mean and standard deviation of depression score in the intervention group was significantly reduced in the post-intervention phase (28.94 ± 15.21) as compared to the pre-intervention phase (99.13 ± 92.37) ($p < 0.001$).

The results showed that the mean age of mothers in the control and intervention groups was 33.73 and 35.95 years, respectively. The possible age range was 19 to 58 years. Approximately, 62.2% of mothers in the control group and 55.6% of them in the intervention group had under diploma education. Also, mothers in the control and intervention groups were housewives in 71.1% and 91.1% of cases, respectively. The duration of leukemia ranged from 2 months to 60 months. With regard to the sex variable, the majority of children in the intervention (57.8%) and control (73.3%) groups were boys. Concerning birth rank, they were the first child in the control and intervention groups in 40%. With regard to the ethnicity variable, the mothers of the control and intervention groups had Baloch ethnicity in 84.4% and 60% of cases, respectively.

Results also show a reduction in the mean and standard deviation of CB scores among mothers of children with leukemia in intervention and control groups from 70.62 ± 13.75 to 55.97 ± 7.16 ($p < 0.001$) and, the mean changes in the post-training CB score in the intervention group were statistically different ($p < 0.001$), but not in the control group ($p = 0.70$) (Tab. 2).

Comparison of the mean CB score among mothers of children with cancer in the intervention and control groups before and after training showed that training could effectively reduce CB among mothers of children with cancer ($p < 0.001$).

Discussion

Comparison of the mean CB scores among mothers of children with cancer in the intervention and control groups before and after training showed that intervention could effectively reduce CB scores among mothers of children with cancer. It seems that the face-to-face training program could significantly reduce CB levels among mothers participating in the present study. In a study of the effect of stress management training on improving the life of mothers with children with leukemia, Manzoomeh et al. [17] showed that stress management can increase the quality of life in the intervention group. In another similar study on the effectiveness of reality therapy on the resilience of mothers with children with cancer, the above researchers also showed that reality therapy training is effective on resilience of mothers with children with cancer [16]. In a study on caregiver burden and its related factors among caregivers in oncology patients, Salmani et al. showed the highest CB score among the spouses. They found that other factors such as low economic status and the disease progression affect CB score [19]. However, this issue has not been addressed in the present study, but it seems that other influential factors should also be addressed in order to manage and control CB. Considering the importance of having a son in Sistan and Baluchestan province, especially in Baloch population, it can be one of the influential factors on increasing CB score. In other words, factors such as ethnicity and sex of a baby as well as support resources and the caregiver age can affect the CB intensity. Therefore, it is necessary to investigate the factors affecting CB intensity taking into account the above variables according to the regional and cultural

status of the mother, especially considering the fact that there are contradictions in some studies in this regard. For example, some studies reported high CB rate among young caregivers [19, 20] (Kim and Given, 2008), but some other studies have reported high CB rate among older caregivers [21]. According to the resources, mothers of cancer children suffer from high CB rate, which can be attributed to their increased responsibility and insufficient attention to caregivers by members of the caregiver team to meet their care needs [22]. The active participation of fathers in treatment programs and their cooperation with mothers in this path may be one of the effective factors that can reduce CB rate among mothers. Although the present study does not address it, the experiences of researchers and dealing with the community of mothers of children with cancer can demonstrate it very well. In the present study, almost all cancer children were cared for by their mothers and fathers played a weak role in this regard. Although the presence of fathers and participation in caring of a sick child may be effective in reducing CB of mothers, it seems that it is necessary to use training methods based on coherent programs that meet all the needs of caregivers. However, the authors could find studies that are inconsistent with the present study.

Limitations

The present intervention investigated the caregiver burden among mothers of children with leukemia. Considering the special conditions of these children, the results cannot be generalized to mothers with children suffering from other chronic diseases.

Conclusions

Considering the foregoing, it seems that it is necessary to use training methods based on coherent programs that meet all the needs of caregivers. In other words, by teaching crisis management strategies and training to control stress, anxiety and creating a sense of efficiency in mothers, their psychological condition can be improved and this process will ultimately lead to a reduction in their caregiver burden. Therefore, it is suggested to address participatory role of fathers in the caregiver burden of mothers in future studies. It is also recommended to address the factors affecting the caregiver burden according to regional conditions in further comprehensive research so that we may implement methods to reduce the caregiver burden of mothers by accurately recognizing and gaining a broader and more comprehensive view of these variables in future planning.

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Conflict of interest

The authors have declared no conflicts of interest.

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ORIGINAL ARTICLE

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Prognosis of gastric cancer patients with paraaortic lymph node metastasis versus those with distant metastases

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ABSTRACT

Introduction. It has long been thought that cases of advanced gastric cancer with paraaortic lymph node (PALN) metastasis are impossible to cure. However, several recent reports on the long-term survival of patients with PALN metastasis have reported an increase in the use of gastrectomy with extended lymphadenectomy, involving the dissection of more nodes than those invaded by the tumour, as the standard surgery for advanced gastric cancer.

Material and methods. The records of 1,015 patients with a confirmed histologic diagnosis of gastric cancer had been reviewed. Among patients with stage IV gastric cancer, 38 had PALN metastasis compared with 233 with peritoneal dissemination and 77 with hepatic metastasis.

Results. Based on tumour location, metastasis to the PALNs was more common in upper-third cancer ($p < 0.01$); hepatic metastasis was more common in well-differentiated adenocarcinoma, and peritoneal dissemination was more common in poorly differentiated cancer ($p < 0.001$). The 5-year survival in patients with metastasis to the PALNs was significantly higher (28.2%) than in patients with peritoneal dissemination (5.2%) or hepatic metastasis (12.0%) ($p < 0.01$).

Conclusions. The results reveal a better 5-year survival associated with gastric cancer patients with PALN metastasis as compared with those with other distant metastases. Therefore, performing a more extended lymphadenectomy in patients with gastric cancer is recommended, especially those with suspected metastasis to the PALNs.

Key words: gastric cancer, paraaortic lymph node, survival

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Introduction

The prognosis of gastric cancer patients with paraaortic lymph node (PALN) metastasis is very poor, even after curative resection combined with systematic PALN dissection. PALN metastasis from gastric cancer is classified as distant metastasis in both the 7th classification of the International Union against Cancer [1] and the 3rd English edition of the Japanese Gastric Cancer Classification [2].

In Korea and Japan, gastrectomy with extended lymphadenectomy, involving the dissection of more nodes than those invaded by the tumour, has recently become the standard surgery for advanced gastric cancer. It was reported that there is a need for a critical application of PALN dissection as one modality of multidisciplinary treatment in patients with advanced gastric cancer in whom PALN metastasis is strongly suspected preoperatively [3].

This study examined the significance of PALN dissection in patients with advanced gastric cancer and evaluated the survival of patients with metastasis to the PALNs, compared with other distant metastases.

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Table 1. Clinicopathologic features of gastric cancer patients with metastasis to paraaortic lymph node, peritoneal dissemination and hepatic metastasis

Variables	Group I (n = 38) (%)	Group II (n = 233) (%)	Group III (n = 77) (%)	p value
Age [mean, year]	54.4	53.7	58.0	NS
Gender				< 0.01
Male	24 (63.2)	157 (67.4)	67 (87.0)	
Female	14 (36.8)	76 (32.6)	10 (13.0)	
Tumor size [mean, cm]	6.2	7.0	6.1	NS
Tumor location				
Upper	**21 (55.3)**	17 (7.3)	8 (10.4)	< 0.001
Middle	12 (31.6)	58 (24.9)	13 (16.9)	
Lower	3 (7.9)	123 (52.8)	**52 (67.5)**	
Whole	2 (5.3)	**35 (15.0)**	4 (5.2)	
Histologic type				< 0.001
Well-differentiated	4 (10.5)	15 (6.4)	**17 (22.0)**	
Moderately differentiated	9 (23.7)	35 (15.0)	30 (38.9)	
Poorly differentiated	17 (44.7)	**138 (59.2)**	21 (27.3)	
Mucinous	3 (7.9)	13 (5.6)	5 (6.5)	
Signet ring cell	5 (13.2)	14 (6.0)	0 (0.0)	
Others	0 (0.0)	17 (7.3)	4 (5.2)	
Borrmann type				< 0.01
I	3 (7.9)	13 (5.6)	4 (5.2)	
II	2 (5.3)	9 (3.9)	8 (10.4)	
III	30 (78.9)	146 (62.7)	58 (75.3)	
IV	3 (7.9)	**65 (27.8)**	7 (9.1)	

NS — not significant

Material and methods

This study reviewed 1,015 gastric cancer patients, who underwent gastric resection at the Division of Gastroenterological Surgery, Department of Surgery, Chonnam National University Hospital, over 5 years (2010 to 2015). There were 38 patients with metastasis to the PALNs, 77 with hepatic metastasis, and 233 with peritoneal dissemination. The effects of age, gender, tumour size, tumour location, histologic type, Borrmann type, and survival rate were examined. This study was approved by the Institutional Review Board of the Clinical Research Institute of Chonnam National University Hospital (IRB No: CNUH-2020-379).

Operative type

The surgical procedures used for the patients with peritoneal dissemination included gastrectomy with local excision of the peritoneum, bypass only and exploration. The hepatectomy procedure consisted of non-anatomic limited resections: segmentectomy, left hemihepatectomy, and right hemihepatectomy.

Chemotherapy

Chemotherapy included a variety of drug combinations. The regimens used were 5-fluorouracil, oxaliplatin, and leucovorin (FOLFOX), taxane and cisplatin (TC), and 5-fluorouracil and cisplatin.

Statistical analysis

The data were analysed statistically using the chi-squared test. The overall survival rates were calculated using the Kaplan-Meier method, and the differences between the curves were tested using the log-rank test. A p-value < 0.05 was considered statistically significant.

Results

Among the 1,015 patients diagnosed with gastric cancer who underwent surgery in the hospital within the study period, 38 patients (3.7%) were diagnosed with PALN metastasis. Table 1 describes the clinicopathologic features of these 38 patients (Group I), the

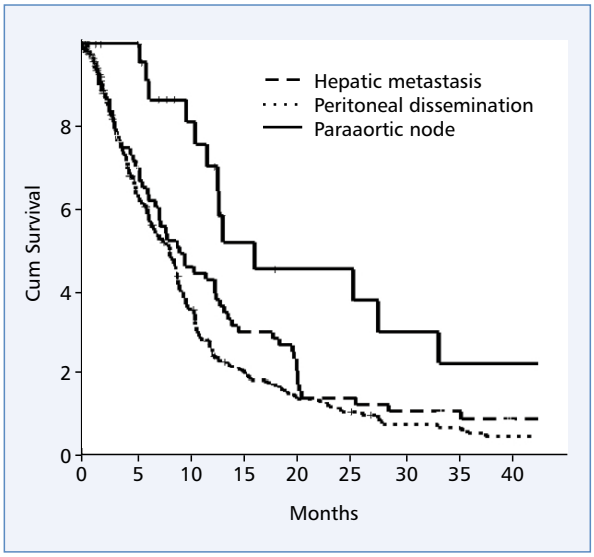

Figure. 1. The Kaplan-Meier survival curves for patients with paraaortic lymph node metastasis, peritoneal dissemination, and hepatic metastasis. The 5-year survival rate for patients with metastasis to the paraaortic lymph node was significantly higher (28.2%) than with peritoneal dissemination (5.2%) and hepatic metastasis (12.0%) ($p < 0.01$)

233 patients with peritoneal dissemination (Group II), and the 77 patients with hepatic metastasis (Group III).

There was no significant difference in the mean age of the patients with PALN metastasis (54.4 years) as compared with patients with peritoneal dissemination (53.7 years) or hepatic metastasis (58.0 years). Among the 38 patients with PALN metastasis, 24 (63.2%) were male and 14 (36.8%) were female. There were more males than females in each group (I = 63.2%, II = 67.4%, III = 87.0%) ($p < 0.01$). There was no significant difference in the mean tumour size (I = 6.2 cm, II = 7.0 cm, III = 6.1 cm). According to tumour location, metastasis to the PALNs was more common in upper-third cancer ($p < 0.01$), peritoneal dissemination was more common in patients with cancer involving the entire stomach, and hepatic metastasis was more common in lower-third carcinoma of the stomach ($p < 0.01$). According to the histologic type, there was no significant difference in patients with PALN metastasis. Peritoneal dissemination was more common in poorly differentiated adenocarcinoma and hepatic metastasis was more common in well-differentiated adenocarcinoma ($p < 0.001$). Peritoneal dissemination was more common in Borrmann type IV gastric cancer (I = 7.9%, II = 27.8%, III = 9.1%) ($p < 0.01$). The 5-year survival rate of Group I was significantly higher (28.2%) than that of Groups II or III (II = 5.2%, III = 12.0%) (Fig. 1) ($p < 0.01$). The median progression-free survival was 22.7 months in Group I, and 6.5 months in Group II, and 11.8 months in Group III.

Discussion

The prognosis of gastric cancer patients with paraaortic lymph node (PALN) metastasis is very poor, even after curative resection combined with super-extended lymph node dissection. Prophylactic PALN dissection has been the standard of care since occult metastasis had occasionally been observed in lymph nodes until a Japanese prospective randomized trial investigating the efficacy of prophylactic PALN dissection showed no survival advantage of PALN dissection for patients with locally advanced gastric cancer and no additional improvement in mortality and morbidity rates after PALN dissection [4, 5]. Since then, PALN dissection has not been routinely performed for patients with advanced gastric cancer. Thus, the significance of PALN dissection in patients with advanced gastric cancer was examined and the survival of patients with metastasis to the PALNs was evaluated, and compared with other distant metastases.

The incidence of pathological metastasis to the PALNs has been reported to vary from 1.4% to 30% [5–8]. Some authors reported that micrometastases were detected by immunohistochemical staining in 64% of patients who underwent prophylactic PALN dissection [9]. In accordance with previous reports, the incidence of pathological metastasis to the PALNs made up 3.7% of all cases in the present study.

The appropriate treatment strategy for gastric cancer patients with PALN metastasis has been a controversial one, and the Gastric Cancer Treatment Guidelines do not provide any treatment recommendations regarding chemotherapy or surgical resection in gastric cancer patients [10]. A multi-institutional prospective randomized controlled trial comparing standard D2 dissection versus D2 plus PALN dissection for serosa-positive advanced gastric cancer without gross metastasis to the PALNs was conducted in Japan. This trial demonstrated that the 5-year overall survival rates did not differ between the two groups and concluded that prophylactic PALN dissection is not effective [5].

In contrast to their result, some investigators reported that PALN dissection for advanced gastric cancer was effective, especially when it was done prophylactically [7] and when the number of paraaortic lymph node metastases were two or less [11]. It was reported that D2 lymph node dissection plus PAND may improve the overall survival for gastric cancer patients in the N3 stage [12]. Morita et al. also reported that rigorous and careful selection of patients can provide long-term survival after systemic lymph node dissection [8].

Many investigators have reported that aggressive surgery (such as extended lymph node dissection) increased operative morbidity and mortality. The Dutch trial did not recommend a routinely extended lymph node dissection because of the high operative morbidity and mortality [13]. Conversely, some authors demonstrated that the overall postoperative complications and death rates did not increase after extended lymph node dissection and they encouraged performing extended lymph node dissection in patients with advanced gastric cancer [14, 15]. De Manzoni et al. reported 2.7% postoperative morbidity with PALN dissection in patients with advanced gastric cancer [16]. It was stated that the morbidity associated with super-extended paraaortic lymphadenectomy could be minimized by very careful manipulation during dissection of the paraaortic lymph nodes, by fine and thorough ligation of the retroperitoneal tissue to prevent lymphorrhea [17]. In the current study, the postoperative mortality for gastric cancer patients with PALN dissection was acceptable. One postoperative death occurred after resection. There was a 2.6% mortality rate, which is consistent with that reported previously.

The reported postoperative 5-year survival rate of patients with pathologically-positive PALNs is 16–25% [3, 5, 6, 10, 18–20]. With several reports of long-term survival in cases with PALN metastasis, Korean and Japanese surgeons are increasingly performing extensive surgery to treat advanced gastric cancers. Several investigators reported that gastrectomy with extended lymph node dissection improves the prognosis of patients with PALN metastasis, and they recommended removing the PALNs when the surgeon detects metastasis there intraoperatively [21–23]. In the presented study, the 5-year survival rate was 28.2% for patients with PALN metastasis.

In this context, the identification of prognostic factors for patients with PALN metastasis seems important. However, it has not yet been well investigated. Previous studies have indicated prognostic factors for these patients: the macroscopic type, overall number of involved nodes [19], number of PALN metastases [10], age of patients and site of PALN metastasis [8]. However, most of these studies included few patients. In this retrospective study, prognostic factors were not investigated because of the small sample size.

Conclusions

In conclusion, the presented study results showed that gastric cancer patients with PALN metastasis survived longer than patients with other types of distant metastases (such as peritoneal dissemination and hepatic metastasis). Therefore, the authors recommend performing a more extended lymphadenectomy in patients with advanced gastric cancer, especially those suspected of metastasis to the PALNs.

Conflict of interest

The authors have declared no conflicts of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Potential role of BRCA1 protein expression as a prognostic tissue biomarker in breast carcinoma: an immunohistochemical and clinicopathologic study from South India

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ABSTRACT

Introduction. BRCA1 dysfunction is a hallmark of both hereditary and sporadic breast cancer. BRCA1 protein expression can be lost by germline mutation, somatic mutation or promoter hypermethylation. This study aimed to explore BRCA1 dysfunction in breast cancer patients by immunohistochemistry and to study its association with prognostic factors.

Material and methods. BRCA1 protein expression was assessed by immunohistochemistry on formalin fixed paraffin embedded tissue blocks of 110 invasive breast carcinoma patients. Furthermore, the clinical findings and tumor features associated with BRCA1 dysfunction were characterized.

Results. Reduced BRCA1 immunoreactivity was observed in 19% of breast cancer cases. Although these patients presented with aggressive tumor characteristics, statistical significance was observed only with presence of lymphovascular emboli ($p < 0.05$). These results suggest that loss of BRCA1 protein expression is associated with an aggressive phenotype of breast carcinoma.

Conclusions. Immunohistochemistry for BRCA1 protein expression in tumor tissues may provide a less expensive screening tool to identify BRCA1 dysfunction due to genetic or epigenetic alterations.

Key words: breast cancer, BRCA1, biomarker, immunohistochemistry, PARP inhibitor

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Introduction

Breast cancer is a highly heterogeneous disease with different biological behaviors, therapeutic responses, and clinical outcomes among the various subtypes. The highly penetrant breast cancer susceptibility gene *BRCA* was discovered in the early nineties which accounts for almost 60% of hereditary breast cancers [1]. Our knowledge on breast carcinogenesis comprising of morphological, immunohistochemical and molecular characterization has improved ever since the discovery of these genes.

BRCA1 gene is located on chromosome 17q21 which consists of 23 coding exons and encodes a nuclear protein with 1863 amino acids [2]. They are tumor suppressor genes encoding proteins that are essential

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in the maintenance of genome stability through repair of double stranded DNA breaks by error free homologous recombination pathway. Therefore, cells that lack BRCA proteins are unable to repair these defects. This deficiency results in the repair of these DNA lesions by potentially mutagenic mechanisms such as non-homologous end joining and single- strand annealing. Several other genes like *EMSY*, *RAD51C*, *ATM* and Fanconi anemia genes are also involved in homologous recombination mediated DNA repair. Pathogenic mutation in these genes is also associated with breast and ovarian cancer predisposition [3].

It is important to note that, in addition to germline *BRCA1* gene mutations, BRCA protein deficiency can be seen in sporadic breast cancers due to somatic mutations or epigenetic *BRCA* gene silencing as a consequence of promoter hypermethylation [4]. This concept is referred to as *BRCA*ness where histopathological and molecular features like triple negative phenotype will be similar to *BRCA1/2* germline mutation-related breast cancers. Genetic aberrations in other homologous recombination-related genes could also lead to *BRCA*ness [5].

Individuals are selected for genetic testing based on clinical characteristics where there is a high chance of missing potential germline mutation carriers due to small families, inheritance through unaffected men and development of tumors at an older age. Also genetic testing offered nowadays is time consuming and expensive. Moreover, this does not identify other mechanisms of BRCA protein deficiency. So the need arises to develop and validate new tissue biomarkers for the detection of BRCA dysfunction. Immunohistochemistry is a cost-effective method which can be used as a screening test for the detection of BRCA dysfunction. Only very few studies have been done all over the world depicting loss of BRCA protein expression by immunohistochemistry. Studies using immunohistochemistry for genetic screening has not been conducted in Southern part of India so far.

The purpose of this study was to identify breast cancer patients with BRCA1 dysfunction by immunohistochemistry and to investigate its association with various clinicopathologic factors. This information obtained will help us in elucidating if clinical, morphological and immunohistochemical features could predict BRCA1 dysfunction in breast cancer.

Material and methods

The present study was conducted over a period of one year between March 2019 and March 2020 in a Tertiary Care Center in Kerala, South India after obtaining approval from the Institutional Ethics Committee (PIMSRC/E1/388A/33/2014). This study was composed of 110 women with a diagnosis of breast carcinoma selected from the Department of Pathology of the Institute. Patients with a histopathological diagnosis of invasive breast carcinoma were included in the study. Mesenchymal tumors, lymphomas, prior treatment elsewhere, those with recurrence and patients not consenting for genetic analysis were excluded from the study.

Informed consent was obtained from all the participants involved in the study. Epidemiological data such as age at diagnosis, personal history of cancer, family history of cancer were obtained from these patients using a prestructured questionnaire.

Histopathologic parameters such as tumor subtype and grade were evaluated using H&E stained slides. Tumor grade was assessed using the Nottingham histological score.

Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections using anti-BRCA1 antibodies (Biogenex, Rabbit polyclonal antibody). Three micrometer-thick sections were obtained on charged slides and incubated at 60–70C for 30 minutes. This is followed by deparaffinization and hydration through descending grades of alcohol. Antigen Retrieval was done with TRIS EDTA buffer for 15–20 minutes. The slides were then rinsed in distilled water and Tris buffered saline 2 minutes each. An endogenous peroxidase blocking agent (3% H2O2) was added for 10 minutes on the section. The slides were incubated with primary antibody and were conjugated with streptavidin Horse Radish Peroxidase (HRP). Diaminobenzene tetrahydrochloride (DAB) was used as the chromogen. The slides were counterstained with hematoxylin and examined under the microscopy. The reaction was considered positive if more than 10% of the cells showed distinctive nuclear staining [6]. The stromal cells served as internal positive control as they retain a normal copy of *BRCA1*.Slides without the primary antibody were used as negative control.

Hormone receptor (estrogen and progesterone) expression, HER2/neu overexpression and Ki-67 proliferation were also studied by immunohistochemical staining on formalin fixed paraffin embedded tissues. Estrogen and progesterone receptors were considered positive when ≥ 1% of cell nuclei were positively stained. For Her2/neu testing, only complete circumferential membranous staining in >10% of tumor cells (score of 3) were considered positive. Ki67 was considered high if more than 20% of cells showed positive nuclear staining.

Clinical parameters studied included patient age at initial diagnosis, size of the tumor, status of regional lymph nodes and the number of lesions at the time of diagnosis.

Association between BRCA1 immunohistochemical status and clinicopathological factors were evaluated using Fisher's Exact Test and $\chi 2$ test.

Results

Patient characteristics

Women studied were in the age group ranging from 31 to 96 years. Mean age at the time of visit was 55.9 years (SD = 11.3). The highest number of breast cancer cases were in the age group 51–60 years which was around 35% followed by 29% each in the age group 41–50years and above 60 years. Approximately 7% were diagnosed under 40 years of age.

Family history of cancer was seen in six patients. One patient presented with two primary cancers. Ten patients presented with multifocal tumor in the same breast. Axillary lymph node metastasis was noted in 42% of cases. Tumor size more than 2 cm was observed in 75% of cases.

Histopathological characteristics

The predominant histological type was invasive carcinoma of no special type (NST) which was seen in 89% of cases. Histological grading of the tumors was done which revealed 30% of grade 1 tumors, 51% grade 2 tumors and 15% of grade 3 tumors. Metaplastic carcinoma of breast was not graded. Hormone receptor positivity was seen in 68% of tumors. HER2/neu overexpression was observed in 16% of tumors. Seven percent of tumors were triple positive (ER+, PR+, HER2+ve) and 23% of tumors were triple negative (ER-, PR-, HER2-ve). Our study showed a high Ki67 expression in 54% of cases (Tab. 1).

BRCA1 immunohistochemistry findings

Of the 110 breast cancer cases, 19% (21/110) showed loss of BRCA1 expression and 81% (89/110) showed intact BRCA1 nuclear staining (Tab. 2). All the cases showed cytoplasmic positivity. Cases with intact BRCA1 staining showed moderate to strong staining in >10% of tumor nuclei (Fig. 1). Majority of the cases showed strong staining in more than 50% of tumor cells. Cases with loss of BRCA1 expression showed either complete absence of staining or weak staining in < 10% of tumor nuclei (Fig. 2).

Clinical and histopathological characteristics of women with altered BRCA1 expression

Of the 21 breast cancer cases with loss of BRCA1 expression, nine were below 50 years of age. 11 patients with altered BRCA1 expression had axillary lymph node metastasis. Fifteen patients presented with tumor size more than 2 cm. None of the cases had family history of cancer. The histological type seen in 20 cases with altered BRCA1 expression was invasive carcinoma of no special type. Among the cases with

Table 1. Clinical and pathological characteristics of the study participants

Parameters	Number of cases (n = 110)	Percentage
Age at initial diagnosis		
< 40 yrs	9	7%
41–50 yrs	31	29%
51–60 yrs	39	35%
> 61 yrs	31	29%
Family history	6	5%
Lymph node metastasis	46	42%
Histological grade		
Grade 1	33	30%
Grade 2	56	51%
Grade 3	16	15%
Histological type		
Invasive breast carcinoma of no special type (NOS)	89	80%
Invasive carcinoma with medullary features	4	3.6%
Invasive lobular carcinoma	3	2.7%
Metaplastic carcinoma	4	3.6%
Mucinous carcinoma	3	2.7%
Invasive papillary carcinoma	2	1.8%
Apocrine carcinoma	1	0.9%
Others (mixed tumors)	3	2.7%
Tumor size		
< 2 cm	82	75%
> 2 cm	28	25%
Lymphovascular emboli	27	25%
Estrogen receptor (ER)		
Positive	75	68%
Negative	35	32%
Progesterone receptor (PR)		
Positive	71	65%
Negative	39	35%
HER2 overexpression		
Positive	9	22.5%
Negative	31	77.5%
Ki67 expression		
High	59	54%
Low	51	46%

Table 2. Proportion of breast cancer patients with reduced BRCA1 expression

BRCA1 protein expression	Number of cases (n = 110)	Percentage
> 10% (Retained)	89	81%
< 10% (Loss)	21	19%

NORMAL BRCA1 IMMUNOREACTIVITY

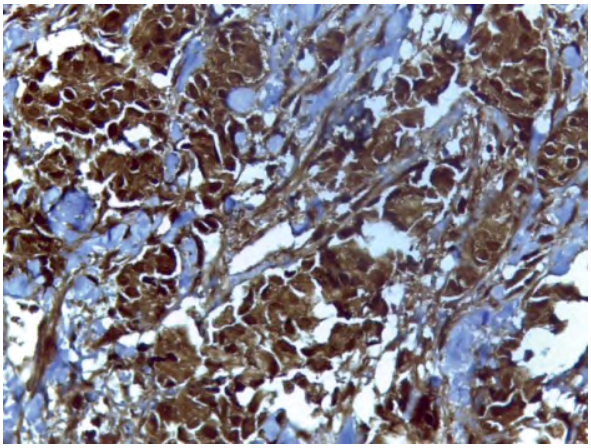

Figure 1. Retained BRCA1 protein expression in tumor nuclei, 40× (normal)

ALTERED BRCA1 IMMUNOREACTIVITY

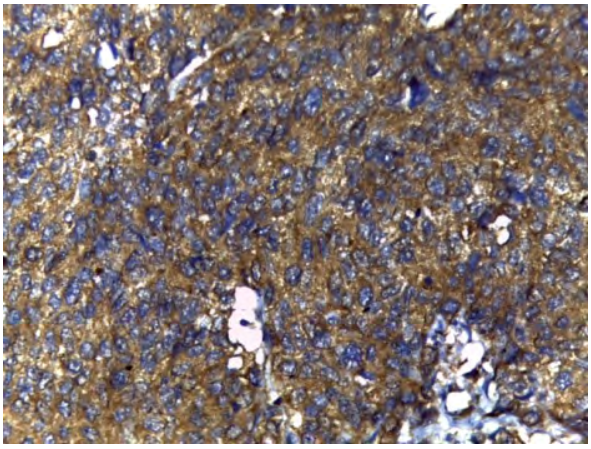

Figure 2. Loss of BRCA1 protein expression in tumor nuclei, 40× (abnormal)

loss of BRCA1 expression, 14 were grade 2 tumors and 5 grade 3 tumors. Triple negative breast cancer was observed in six cases and Her2/neu overexpression in two cases. Lymphovascular emboli was observed in 9 cases. Ki 67 expression was high in sixteen cases with altered BRCA1 expression.

Statistical significance

It was observed that presence of lymphovascular emboli showed association with loss of BRCA1 expression statistically ($p \leq 0.05$). All other clinicopathologic variables (family history, number of lesions, histological grade, stage, hormonal receptor and HER2/neu expression, Ki67) were not found to be statistically significant.

Discussion

Breast cancer is the most commonly diagnosed cancer in females with an incidence of 2.3 million cases, representing 11.7% of all cancer cases and 6.9% of all cancer related deaths in 2020 [7]. The state of Kerala in South India has been seeing a rise in the number of breast cancer cases over the last few years [8]. Moreover, a good number of cases in India are seen in younger age groups when compared to women in western countries [9]. This stress the importance in identifying the cause for the current trend in the state. Genetic predisposition is one of the reasons for early onset breast cancer which is usually aggressive in nature. *BRCA1* is the most commonly mutated gene in hereditary breast cancer. Genetic testing for germline mutation is not routinely done in most Indian centers due to the high cost involved. This has urged the need to identify and validate new tissue biomarkers for prognostic and therapeutic purposes. The role of BRCA1 protein in tumor tissues can be investigated in these patients by immunohistochemistry where genetic testing cannot be performed. Immunohistochemistry is a cost effective, easy to perform laboratory method to assess the expression of various proteins in tumor tissues for diagnosis, localization and detection of dysfunctional proteins. Several studies have also reported other mechanisms such as somatic mutation and promoter hypermethylation for reduced BRCA protein expression in tumor tissues [10].

The benefit of identification of BRCA gene mutations has been well established over the years. Novel targeted therapies such as Poly-(ADP) ribose polymerase inhibitors (PARPi) and platinum based chemotherapeutic agents have been developed for BRCA associated cancers [11]. Olaparib and talazoparib are the PARP inhibitors currently approved for treatment in patients with advanced breast cancer associated with germline BRCA mutation [12]. Although the use of PARP inhibitors is currently restricted to germline BRCA mutated breast cancers, trials are underway evaluating its role in the management of breast cancers exhibiting BRCAness phenotype and homologous recombination deficiency [13]. Recent studies have shown promising results regarding the use of PARP inhibitors in sporadic breast cancers with BRCA dysfunction.

Large number of studies have been done on BRCA gene mutation in breast cancer worldwide. However, BRCA1 protein expression in tumor tissues of breast cancer patients is less known. This study was therefore undertaken to assess the expression of BRCA1 protein in female breast cancer patients from Kerala and to investigate its association with clinical and pathological factors. The aim of this study was to detect BRCA1 dysfunction and identify tumor characteristics relating to dysfunction in formalin-fixed paraffin-embedded tissues.

In the current study, we identified 19% of women with altered BRCA1 protein expression in tumor tissues. Majority of women showed intact BRCA1 staining in the tumor tissues. We observed both nuclear and cytoplasmic staining in all the cases. Our results also demonstrated that loss of BRCA1 expression was associated with aggressive tumor characteristics. The breast carcinomas with reduced BRCA1 expression were high grade tumors. Seventyone percent of cases with altered expression had large tumor size. Triple negative phenotype was observed in 29% of tumors with altered expression. Another interesting observation was that 43% of women with reduced BRCA1 expression were below 50 years of age.

According to a recent study by Israa A Hussein et al. [14], BRCA1 protein expression was reduced in 79.5% which is quite high when compared to our study. They demonstrated a significant relationship of BRCA status with advanced stage, higher grade of the tumor and hormone receptor negativity. Priyadarshini et al. reported absence of BRCA1 staining mostly in tumors of large sizes and with higher histologic grades [15]. These findings are in line with our study.

Deepti Verma et al. observed a significant association of reduced BRCA1 expression with HER2/neu positivity. We observed HER2/neu overexpression in 10% cases with reduced expression. In addition, they also showed association of altered expression with large tumor size and high-grade tumors which was statistically significant [16]. These findings are similar to the observations seen in our study.

Another study done in Portugal where BRCA1 immunohistochemistry was done using monoclonal antibodies and was correlated with BRCA1/2 genetic screening results. This study showed loss of BRCA1 expression in 80% of cases with germline BRCA1 mutation indicating high specificity for the prediction of BRCA1 carriers with immunohistochemistry using monoclonal antibodies [17]. Different types of antibodies for BRCA1 proteins are commercially available at present. Controversies regarding the subcellular localization of BRCA1 have been existing for the last few years. Formalin fixed paraffin embedded sections of breast cancer showed a variety of staining patterns ranging from predominantly nuclear, both nuclear and cytoplasmic and mainly cytoplasmic. This variability in the subcellular localization of BRCA1 protein could be due to the specificity of the antibodies used in various studies to detect the protein. In our study we used a polyclonal antibody which showed both nuclear and cytoplasmic positivity.

Kazuaki Miyamoto et al. [4] observed reduced BRCA1 immnoreactivity in 62% of sporadic breast cancers where none of the cases harbored BRCA1 mutations thereby showing other mechanisms like promoter hypermethylation as the cause for the reduced expression. Another study by Hedau et al also observed a decline in the protein expression of BRCA1 in 50% of sporadic breast cancer cases [18].

Wen-Ying Lee [19] reported a higher incidence of loss of BRCA1 nuclear expression in younger women with breast cancer which was seen to be associated with large tumor size and high proliferation rate. This observation is consistent with our study findings where 43% of the cases with reduced BRCA1 expression were below 50 years.

Rakha et al. [20] showed complete loss of BRCA1 nuclear expression in 15% of breast cancer cases which was correlated with high-grade, advanced lymph node stage, larger size, vascular invasion, negative estrogen and progesterone receptor.

Similar findings were also observed in a Japanese study by Yoshikawa et al. [21] where 28% of sporadic breast cancer cases also showed reduced BRCA1 expression in addition to 79% of *BRCA1* associated breast cancers.

Several studies have been done on BRCA1 protein expression in ovarian cancers also in the past. According to a study by J. L. Meisel et al. [22], BRCA1 immunohistochemistry was found to be abnormal in 36% of ovarian cancers of which 52% was due to germline mutation and the remaining due to somatic mutation and promoter hypermethylation. Two other similar studies done by Karuna Garg et al. and Tarinee Manchana et al. on ovarian cancer patients also showed loss of BRCA1 expression by immunohistochemistry in 47% and 20% of cases [23, 24].

Therefore, our study demonstrated BRCA1 dysfunction in tumor tissues of a subset of breast cancer cases which was seen to have tumor characteristics like higher grade, high proliferative index, large tumor size and presence of lymphovascular emboli. Reduction of BRCA1 protein expression may be considered as an additional prognostic factor. Our study indeed has limitations as we were unable to obtain the mutation status in these patients. It is imperative to conduct large scale studies to assess the clinical usefulness of immunohistochemistry as an alternative to the more expensive molecular testing especially in low resource settings and also to select patients likely to benefit from targeted therapies.

Conclusions

In summary, immunohistochemistry is a promising tool in detecting loss of BRCA1 protein expression which could be due to genetic or epigenetic alterations. Reduced or loss of BRCA1 protein expression plays a significant role in the development of breast cancer. Majority of the cases with loss of protein expression presented with aggressive tumor characteristics. These findings indicate that there are tumor characteristics which suggest the presence of BRCA1 dysfunction in breast cancer patients. Thus, knowledge of BRCA1 expression in tissues could provide additional clinically relevant information in breast cancer patients.

Ethical approval and consent to participate

The study was done after obtaining approval from the Institutional Ethics Committee (No.PIMSRC/E1/388A/33/2014) of Pushpagiri Institute of Medical Sciences, Tiruvalla, Kerala, India.

Informed consent to participate in the study has been taken from all the study subjects.

Consent for publication

Consent has been taken from the participants for publishing their clinical details and other relevant data in journals.

Availability of data and materials

All data generated or analyzed during this study are included in this article for publication.

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Authors' contributions

Dr Reeba Mary Issac: data collection, manuscript writing — original draft preparation, investigation, software. Dr Prema Saldanha: conceptualization and design of the work, methodology, critical revision of the article. Dr Jessy M.M: conceptualization and design of the work, supervision, review and editing, validation. Dr Rebecca Mathews: methodology. Dr Bindu Kumari: methodology. Dr Tiju Chacko: methodology, writing — review and editing.

Conflict of interest

The authors have declared no conflicts of interest.

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ORIGINAL ARTICLE

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Perceived spouse unsupportive behaviors in women with breast cancer and their spouses

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ABSTRACT

Introduction. Unsupportive responses from relatives, particularly spouses, play a significant role in the psychological adjustment of breast cancer patients and their spouses. Failure to meet the physical and psychological needs of breast cancer patients and their spouses can lead to anxiety, depression, and numerous marital problems. The aim of this study was designed to describe perceived spouse unsupportive behaviors in women with breast cancer and their spouses.

Material and methods. This is a cross-sectional study. A total of 220 women with breast cancer along with their husbands participated in this study through random sampling. In the present study, data collection was performed using a demographic information checklist and a questionnaire.

Results. The mean perceived women's unsupportive behavior (20.73 ± 8.44) was higher than that of men's (18.80 ± 5.83), which was statistically significant ($p = 0.003$). The mean score of perceived women's unsupportive behavior in the categories of marital status, companion, place of residence, men's and women's occupation, and the type of residential house, and the mean score of perceived men's unsupportive behavior in the category of current treatment were different.

Conclusions. Women perceive their spouses' behaviors as less supportive than their spouses' perceptions of women's behavior, which highlights the need for husbands to be more attentive to the impact of their behavior on their wives. Furthermore, talking with each other about problems is the most imperative factor in perceiving support by couples; accordingly, it can be concluded that couples who are reluctant to talk to each other concerning the problem perceive less mutual support.

Key words: unsupportive behavior, breast cancer, nursing, spouse

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Introduction

Breast cancer is one of the most prevalent and disturbing health problems of women worldwide [1]. It comprises 30% of gynecological cancers [2]. This type of cancer is the second leading cause of mortality in developed countries and the third cause in less developed countries [3]. Approximately 41,000 women lose their lives each year as a result of breast cancer [4]. As reported by the World Health Organization (WHO),

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by 2050, 3.2 million women will develop breast cancer, yet in current statistics, 1 in 8 women suffer from this type of cancer (12.5%) [5].

Over recent decades, research has examined individuals' perceptions of cancer consequences. In addition to the physical effects, the psychological and social impacts have been realized [6]. Numerous supportive intervention strategies have been developed to help cancer patients deal with their problems during the disease course. The cancer incidence influences both patients and their closest relatives and might be manifested in various mutual behaviors in patients and their spouses. This experience may create stress in the spouse, resulting in their loss of emotional, social, and economic support to the patient and can have an impact on their daily life and behavior [7]. One of the principal consequences of a spouse's cancer diagnosis is anxiety, particularly a depressive state. Mood disorders in the spouse are closely related to a higher anxiety rate in the cancer patient [8]. Breast cancer diagnosed in women at a young age (under the age of 50) causes higher rates of health and social problems than in women diagnosed at an older age [8, 9].

Spouses are considered the best source of support for cancer patients [10]. Nevertheless, providing support may be challenging for spouses due to their anxiety or the impact of breast cancer on their relationship [11]. A supportive spouse may assist the patient to psychologically adjust to his or her illness. However, imperfect support can result in dissatisfaction, depression, and anxiety [12, 13]. Perceived unsupportive behavior is relatively uncommon yet excessively challenging due to the fact that it is significantly associated with anxiety in patients with cancer [14]. Previous studies indicate that spouse unsupportive behavior is a predictor of a higher level of avoidance behavior in patients with breast cancer [14] and is connected with increased anxiety levels [15].

Unsupportive behavior is considered as obviously critical or explicit avoidant behavior [16], and for women, spouse's support is defined as the expectations they have of their husbands. Women often describe their experience of the family's practical work (working, household chores, and child care) and roles in society (emotional tasks, parenting, and building relationships). A supportive spouse provides support equivalent to or beyond their expectations. As defined by these women, unreliable supportive spouses provide support inconsistently, and unsupportive spouses do not provide sufficient support and are reluctant to do so [17]. Persistent avoidant behavior negatively affects women's psychological adaptation to breast cancer [18, 19]. The negative effect of the spouse's avoidant behaviors on the patient's psychological adaptation is greater than the positive effects of the spouse's supportive behaviors [19]. Nevertheless, recognizing the spouse's empathetic feelings, for those who do not escape hardships, reduces their anxiety levels [20]. Marital satisfaction is connected with higher reciprocal support, interdependence, and satisfaction with supportive needs [21]. On the contrary, individuals in unsuccessful marriages do not depend on their spouse as the main support source and seek support outside of marriage [22]. In a broken marriage, couples may have a negative perception of each other's behavior. Women who experienced dissatisfaction with their marital relationships three months after the diagnosis of cancer were expected to be separated or divorced during the 8-year follow-up as compared to women who had satisfactory lives during the first three months of diagnosis [23]. An increase in cancer treatments occurred in women receiving no emotional support from their husbands [24].

The degree of men's unsupportive behavior is strongly associated with their spouse's disease-related behaviors which may reciprocally result in the women unsupportive behavior. This behavior is also related to women's discomfort and maladaptation [14]. Studies have indicated that perceptions of spouse unsupportive behavior is a predictor of more adverse behaviors in patients with breast cancer and is associated with an increase in stress levels [15, 19]. The adverse effects resulting from the spouse's undesirable behaviors on the patient's mental balance surpasses the positive effects of their supportive behaviors [16]. According to Shiozaki et al., problem-avoidance behavior is an effort made to hide worries and anxiety, evade disease-related matters, and the sensitivity to areas that changed following surgery. Therefore, problem-avoidance behaviors have pervasive and extensive effects on patients' mental adaptation. Couples-focused interventions might be enhanced by focusing on reducing couples' problem-avoidance behaviors [20].

Improving health-related behaviors needs to be considered as one of the principal goals in cancer treatment. Certainly, women are one of the rudimentary constituents of the family and society. Subsequently, promoting the lives of women with breast cancer leads to improvement in their survival, enhances their lifestyle, and results in stronger family cohesion [25]. Researchers should focus on the impact of unsupportive behaviors rather than merely on the positive effects and social support. Spouses' unsupportive behaviors have a more significant effect on stress and mental health status compared to supportive behaviors. Receiving the spouse's negative support may increase the patient's negative feelings, including fear or selfishness [26].

Finally, several studies have been conducted on the marital satisfaction of patients with breast cancer, changes in a sexual relationship, intimacy after cancer treatment, the impact of cancer on the family, and the support provided by spouses to women with breast cancer [25]. However, a review of the literature shows that little is known about unsupportive behavior in women with breast cancer and their spouses, description of patients and their differences, and factors influencing couples' perceived unsupportive behavior. Evidently, it is of particular impor-

tance that studies identify and describe patients and the differences between them as well as the influential factors in different societies. The present study was conducted to describe perceived spouse's unsupportive behaviors.

Material and methods

Methods

This cross-sectional study was conducted in Tabriz, Iran in 2020 to describe unsupportive behaviors perceived by women with breast cancer and their spouses. The study was approved by the Vice-Chancellor for Research of Tabriz University of Medical Sciences with ethics code number IR.TBZMED.REC.1398.991.

Participants and setting

Participants included women with breast cancer and their spouses who were recruited at oncology hospitals in Tabriz (Iran) from April to July 2020. Inclusion criteria were being married and suffering from breast cancer or having a spouse with breast cancer. Those suffering from a severe psychological problem and unwillingness to participate in the study were excluded.

There were 440 individuals over the age of 27 years who participated. According to the findings of Manne et al. (2014), regarding an estimate of the mean (standard deviation) of the main variable equal to 16.95 (34 ±0.34), 95% confidence interval, and 15% acceptable relative error of the mean, the minimum sample size was calculated to be 171 couples. The final sample size increased to 220 couples, considering 20% sample attrition.

After receiving the patients' and their spouses' medical files, they were selected randomly (https://www.randomizer.org/), and subsequently, the researcher contacted them and arranged an appointment to meet and complete the questionnaire. It is worth noting that questionnaires were obtained from patients and their spouses separately in different places. Written consent to participate in the study was obtained from 220 eligible couples after the study was explained, including protections related to confidentiality of their information and their right to withdraw from the study at any stage.

Measures

The demographic information checklist collected information about participants including age, residence, education level, occupation, companion, marital status, marriage duration, residence, disease stage, surgery type, current treatment, and time to diagnosis.

The Partner Unsupportive Behavior scale (Manne & Schnoll, 2001) was administered, consisting of 13 items to measure couples' critical and avoidant responses to cancer [27]. Items were rated on a 4-point scale (1 = never responded this way, 4 = often responded this way), and scores ranged from 13 to 52. In this present study, internal consistency for patients and spouses was 0.91. The validity of the questionnaire was evaluated and confirmed through content and face validity by 15 nursing education specialists and ten oncologists after translation-retranslation. The reliability of the questionnaire was determined by test-retest with a two-week interval on 30 individuals and after identifying Cronbach's alpha coefficient (internal consistency) and Intra-class Correlation Coefficient (ICC). Thus, for women's and men's perceived unsupportive behavior were obtained 0.96 (CI 95%: 0.91–0.98) and 0.94 (CI 95%: 0.89–0.96), respectively.

Statistical analyses

To analyze the data, we used SPSS version 16.0 (SPSS Inc., Chicago, IL). Number (percentage) and mean (standard deviation) along with Max-Min values were used to describe variables. The Kolmogorov test with skewness and elongation indices was used to evaluate the normality of the data. In the inferential section, independent t-test, ANOVA, and Chi-square test were used. Furthermore, where the ANOVA test was significant, the Hochberg post hoc test pairwise comparison was used to compare the categories of variables. A significance level of 0.05 was considered significant in all tests.

Results

In this study, in which 220 couples participated, the mean age and the standard deviation were 45.65 ± 9.802 in female and 51.21 ± 10.703 in male participants. The female participants' age ranged between 27 and 83 years, and that of male participants ranged between 28 and 85 years. In addition, the highest percentage of participants (51.4%, 113 individuals) had 1 or 2 children and (95.9%, 211 individuals) lived with their spouses. Most participants' income (135, 61.4%) was fully inadequate for the cost of treatments. Findings also showed that a high percentage of female (72, 32.7%) and male participants (61, 27.7%) had an elementary education level. The majority of female participants (204, 92.7%) were housewives, while male participants (74, 33.6%) were self-employed. The maximum duration of marriage was between 20 and 30 years (78, 35.5%). The most common type of surgery performed on patients (549, 54.1%) was mastectomy, and more than half of patients (125.8, 56.8%) received chemotherapy. Furthermore, most of the participants' disease diagnosis was over 24 months (63, 28.6%), at stage 3 of the disease (91, 41.4%) (Tab. 1).

Table 1. Participants' demographic and disease information (n: 440)

Variables	Categories	Gender	
		Woman (n: 220) N (%)	Man (n: 220) N (%)
Age in years	< 40	56 (25.5)	25 (11.4)
	60–40	141 (64.1)	146 (66.4)
	> 60	23 (10.5)	49 (22.3)
Number of children	0	32 (24.5)	32 (14.5)
	2–1	113 (51.4)	113 (51.4)
	4–3	16 (7.3)	16 (7.3)
	> 5	59 (26.8)	59 (26.3)
Residence	City	157 (71.4)	157 (71.4)
	Village	53 (24.1)	53 (24.1)
	Suburbs	10 (4.5)	10 (4.5)
Marital status	Married	211 (95.1)	211 (95.5)
	Single	7 (3.2)	7 (3.2)
	Divorced	2 (0.9)	2 (0.9)
Type of residential house	Personal	160 (72.7)	160 (72.7)
	On rent	53 (24.1)	53 (24.1)
	Organizational	2 (0.9)	2 (0.9)
	Relatives' house	5 (2.3)	5 (2.3)
Sufficiency of monthly income for treatment	Fully	4 (1.8)	4 (1.8)
	Relatively	81 (36.8)	81 (36.8)
	Not at all	135 (61.4)	135 (61.4)
Education	Illiterate	42 (19.1)	39 (17.7)
	Primary	72 (32.7)	61 (27.7)
	Secondary	37 (16.8)	42 (19.1)
	High school	43 (19.5)	45 (20.5)
	College	26 (11.8)	33 (15.0)
Occupation	House wife	204 (92.7)	–
	Employed	14 (6.4)	–
	Student	1 (0.5)	–
	Retired	1 (0.5)	21 (9.5)
	Unemployed		11 (5.0)
	Employed	–	21 (9.5)
	Laborer	–	60 (27.3)
	Self-employed	–	74 (32.6)
	Farmer	–	17 (7.7)
	Driver	–	16 (7.3)
Companion	Spouse	114 (51.8)	–
	Father	4 (1.8)	–
	Mother	5 (2.3)	–
	Child	25 (11.4)	–
	Relatives	42 (19.1)	–
	No companion	30 (13.6)	–

→

Table 1 cont. Participants' demographic and disease information (n: 440)

Variables	Categories	Gender	
		Woman (n: 220) N (%)	Man (n: 220) N (%)
Duration of marriage (years)	< 10	23 (10.5)	23 (10.5)
	20–10	60 (27.3)	60 (27.3)
	30–20	78 (35.5)	78 (35.5)
	> 30	59 (26.8)	59 (26.8)
Type of surgery	Preserving the breast	90(40.9)	–
	Mastectomy	119 (54.1)	–
	No surgery	11 (5.0)	–
Current treatment	Chemotherapy	125 (56.8)	–
	Radiotherapy	31 (14.1)	–
	Both	8 (3.6)	–
	None	16 (7.3)	–
	Control	39 (17.7)	–
Duration of diagnosis (month)	< 6	55 (25.5)	–
	12–6	54 (24.5)	–
	24–12	48 (21.8)	–
	> 24	63 (28.6)	–
Disease stage	0	7 (3.2)	–
	1	27 (12.3)	–
	2	60 (27.3)	–
	3	91 (41.4)	–
	4	35 (15.15)	–

Due to the normal distribution of unsupportive behaviors in women and their spouses, the mean and standard deviation were used to summarize reported behaviors. The mean perceived unsupportive behaviors in women and spouses were equal to 20.73 (8.44) and 18.80 (5.83), respectively. The confidence intervals of women's unsupportive behaviors and their spouses were 19.61–21.85 and 17.79–7.47, respectively. Moreover, the mean perceived unsupportive behavior in women was higher than that of men, which was statistically significant ($p = 0.003$). On the other hand, considering the cut-off point of 2.5 (median) for each item and the cut-off point of 32.5 for total items, the mean was 2.03 (SD = 0.69), the t-test was 2.95, and the degree of freedom was 438 ($p = 0.003$). The rate of perceived unsupportive behavior in women and their spouses was equal to 22 (10.0%) and 8 (3.6%), respectively. The chi-square test results (after confirming Cochrane conditions and independent random sampling) showed a statistically significant difference between the perceived unsupportive behavior in women and their spouses ($p = 0.008$) (Tab. 2).

Table 3 shows the mean score of women's perceived unsupportive behavior in different marital status categories ($p < 0.001$). The Hatchberg post hoc test results showed that the mean score of unsupportive behavior of patients living in the suburbs was different from other patients, and the mean score of women's perceived unsupportive behavior was different in categories of having a companion ($p < 0.001$). In addition, the mean score of women's perceived unsupportive behavior in different categories of marital status, type of housing, and men's and women's occupation was different from men's perspective ($p < 0.001$). The results of the Hatchberg post hoc test showed that the support mean score of patients who had been referred to the hospital alone was different from other patients. The mean score of support in different age groups, number of children, the sufficiency of monthly income, men's and women's education, and duration of marriage did not show a statistically significant difference ($p > 0.05$). Finally, the mean score of perceived spouse unsupportive behavior in different categories of current treatment was different ($p < 0.001$). The Hatchberg post hoc test results indicated that the mean score of unsupportive behavior in patients of untitled or control categories differed from other patients ($p > 0.05$).

Table 2. Frequency distribution and relative frequency of support questionnaire items (n: 440)

No.	Items	Woman perceived (n/%)				Man perceived (n/%)			
		Never	Rarely	Sometimes	Often	Never	Rarely	Sometimes	Often
1	Seemed impatient with you	111 (50.5)	58 (4.26)	32 (5.14)	19 (6.8)	114 (8.51)	57 (9.25)	34 (5.15)	15 (8.6)
2	Seemed angry or upset with you when they did things to help you	129 (58.6)	52 (23.6)	22 (10.0)	17 (7.7)	127 (57.7)	60 (27.3)	24 (10.9)	9 (4.1)
3	Seemed not enjoy being around you	163 (74.4)	25 (11.4)	13 (5.9)	19 (8.6)	176 (80.0)	24 (10.9)	14 (6.4)	6 (2.7)
4	You had to wait a long time for help when you needed it	128 (58.2)	38 (17.3)	30 (13.6)	24 (10.9)	149 (67.7)	47 (21.4)	15 (6.8)	9 (4.1)
5	Avoided being around you when you were not feeling well	151 (68.6)	31 (14.1)	17 (7.7)	20 (9.1)	174 (79.1)	27 (12.3)	9 (4.1)	10 (4.5)
6	Gave you the idea that they really did not want to talk about the problem you were having	127 (57.7)	39 (17.7)	23 (10.5)	31 (14.1)	149 (67.7)	34 (15.5)	20 (9.1)	17 (7.7)
7	Shouted or yelled at you	146 (66.4)	29 (13/2)	28 (12/7)	17 (7/7)	151 (68/6)	25 (11/4)	33 (15/0)	11 (5/0)
8	Did not seem to respect your feelings	163 (74/1)	36 (16.4)	12 (5.5)	9 (4.1)	187 (85.0)	26 (11.8)	5 (2.3)	2 (0.9)
9	Complained about your illness or about helping you with a task you found difficult to do by yourself	148 (67.3)	43 (19.5)	20 (9.1)	9 (4.1)	146 (66.4)	46 (20.9)	18 (8.2)	10 (4.5)
10	Seemed uncomfortable talking to you about your illness	131 (59.5)	41 (18.6)	17 (7.7)	31 (14.1)	144 (65.5)	49 (22.3)	12 (5.5)	15 (6.8)
11	Criticized the way you handled your disease and/or its treatment	189 (85.9)	19 (8.6)	9 (4.1)	3 (1.4)	203 (92.7)	11 (5.0)	4 (1.8)	1 (0.5)
12	Seemed less accepting of you since you got cancer	169 (76.8)	31 (14.1)	9 (4.1)	11 (5.0)	174 (79.1)	35 (15.9)	7 (3.2)	4 (1.8)
13	Was not emotionally supportive of you, when you were expecting some support	135 (61.4)	41 (18.6)	17 (7.7)	27 (12.3)	155 (70.5)	41 (18.6)	14 (6.4)	10 (4.5)

Tale 3. Distriution of unsupportive ehaviors y demographic characteristics and disease profile in the study participants (n: 440)

Variales	Category	Perceived female support (n: 220)		Perceived male support (n: 220)	
		Mean (SD)	p	Mean (SD)	P
Women's age in years	< 40	20.37 (9.84)	*0.865	18.19 (5.39)	*0.704
	60–40	20.96 (8.27)		18.94 (5.98)	
	> 60	20.21 (5.58)		18.52 (5.13)	
Men's age in years	< 40	21.36 (11.65)	*0.898	17.92 (5.14)	*0.706
	60–40	20.56 (8.40)		18.78 (5.82)	
	> 60	20.91 (6.68)		18.89 (5.84)	
Numer of children	0	17.62 (5.50)	*0.142	18.00 (6.37)	*0.721
	1–2	21.41 (8.91)		19.02 (5.74)	
	3–4	20.06 (6.29)		17.68 (4.14)	
	> 5	21.30 (9.09)		18.78 (5.80)	
Residence	City	20.82 (8.50)	*0.020	18.83 (5.72)	*0.878
	Village	19.24 (6.37)		18.39 (6.12)	
	Suurs	27.30 (13.63)		18.40 (3.92)	
Marital status	Married	20.40 (7.89)	*< 0.001	18.59 (5.65)	*0.254
	Single	23.57 (13.52)		20.42 (7.69)	
	Divorced	46.00 (8.48)		24.50 (7.77)	
Type of residential housing	Personal	20.43 (8.1)	*0.041	18.75 (5.98)	*0.526
	On rent	20.77 (8.68)		18.39 (5.06)	
	Organizational	17.50 (4.94)		15.50 (3.53)	
	Relatives' house	31.20 (14.75)		21.80 (4.65)	
Sufficiency of monthly income	Fully	17.00 (6.16)	*0.334	16.00 (3.55)	*0.465
	Relatively	19.92 (6.21)		18.35 (4.98)	
	Not at all	21.33 (9.56)		19.00 (6.19)	
Women's education	Illiterate	20.02 (6.77)	*0.557	19.07 (6.80)	*0.394
	Primary	21.36 (7.87)		18.55 (4.70)	
	Secondary	21.97 (10.22)		18.59 (6.02)	

SD — standard deviation; *ased on ANOVA analysis of variance; **ased on 2 independent T test samples

Discussion

The present study describes the perceived unsupportive behaviors of women with breast cancer and their spouses. Former studies have indicated that perceived unsupportive behaviors of family members play a central role in a patient's psychological adaptation to cancer. It also influences individuals' adjustment to other challenging life events. Perceived unsupportive behaviors and failure to meet cancer patients' needs and related factors has been shown to affect breast cancer patients' quality of life and their relationship with their spouses [28]. Our study results can yield insight for conducting interventional studies in Iran and elsewhere to improve outcomes for women with breast cancer and their families.

Using the Spouse Unsupportive Behavior Questionnaire, we found the item *Does not want to talk with you about the current problem and talking is annoying for him/her* had the highest percentage, and women and

their spouses reported having perceived the occurrence of this item more than other items in their spouses. A study conducted in Israel found that being close to one's spouse and talking to each other were the best predictors of their quality of life and adaptation [29]. Another study found that regular male communication was based more on not expressing emotions and low intimacy. In contrast, female communication emphasized expressing emotions, greater intimacy, talking, and close communication [27, 30]. These days, there is no difference in expressing feelings by men and women [19, 31], which is similar in our study. In both genders, not talking about the problem is the most common item of perceived unsupportive behavior. This indicates that talking about the problem is of importance for both the patient and the spouse, while the absence of communication can be irritating. The study by Manne et al. similarly states that concerns about disease progression and death need to be addressed and discussed more. Similarly, in male patients, expressing emotions helps them adapt to the disease, feel more support from the other party, and experience less stress [32]. Manne et al., also state that if the spouse perceives unsupportive behaviors, this perception suggests a broken relationship in expressing concerns with that spouse [16].

Our findings show that the mean score of women's perceived unsupportive behavior is higher than that of men's. This indicates that women perceived more unsupportive behavior from men than what men perceived of women's behavior. A study in China found that women with cancer reported higher unmet support needs than men [33]. These findings are consistent with Burg's study [34] and another study conducted in Iran [28]. This high level of unmet support needs reported in studies among women underscores the importance of paying closer attention to expressing gender-specific support needs [33]. In other studies, it has been emphasized that women with ovarian and breast cancer who were on chemotherapy had higher unmet support needs and higher stress levels than men [19, 35]. Another study stated that traditional men's routine behavior is not related to unsupportive behaviors. Studies on gender and support showed that women show more emotional support than their husbands [19], which is similarly stated in the present study and indicates that it is identical in different societies. Another study showed that gender does not predict psychological needs [36], while another states that men have higher unmet supportive care needs than women [37]. Despite the results of previous studies [36, 37], most of which have been conducted in Western countries, it is predictable that Iranian women with cancer experience more psychological support needs.

The present study reveals that factors such as marital status, companion at the time of hospital visits, residence, men's and women's occupation, and type of residential housing affected women's perceived unsupportive behaviors and the factor of current treatment (no treatment or only control) affected men's perceived unsupportive behaviors. A study of young adult cancer patients showed that those individuals with no children had greater levels of psychological, health system/information and physical/daily living unmet needs. Such individuals who were deprived of family support considered cancer to be much more lethal [38], which is consistent with our study. In the present study, there was a significant difference between patients who visited the hospital alone to receive treatment and those visiting with their spouse, parents, or children, and it is an influential factor in the perception of unsupportive behavior.

Moreover, in the present study, unsupportive behavior in individuals who were not currently receiving treatment or only referring for control was significantly different from those receiving chemotherapy or radiation therapy which were among the factors influencing the incidence of unsupportive behaviors due to the passage of time and prolonged disease and stress concerning the future of the disease. [39, 40]

Another study in Japan found that individuals in the chemotherapy phase perceived less support than other patients who did not receive chemotherapy, and their support needs were not met [38]. These results were inconsistent with our study. The difference might be due to a lack of investigation of the association between other treatments and unmet support needs. The researchers also noted that there was not a study on differences in perceptions of support needs of patients receiving treatment compared with those who completed treatment and the type of their treatments. Support needs can change during the transition from cancer treatment to the post-treatment or survival phases [41]. Another study in China found that people who survived long-term cancer had a greater fear of cancer recurrence, which could increase their unmet support needs [42].

Another influential factor was marital life. Divorced individuals had a higher perception of unsupportive behaviors, which was similar to another study conducted in Iran that found sick women living alone were expected to have more unmet support needs. Further, individuals diagnosed with cancer are more prone to marital problems such as divorce after being diagnosed with cancer [28]. Another study conducted in Mexico also confirms the present results [43].

In the present study, marital status, men's and women's occupation, residence, and type of residential housing were among the influential factors of perceptions of women's unsupportive behaviors. These results were moderately consistent with other studies conducted in Iran, in which being married, being a housewife, and living with the spouse and children were mentioned

as influential factors [28]. Furthermore, in another study, cancer patients had more unmet financial support needs [33]. In our study alike, residence and type of residential housing were introduced as influential factors in the category of financial needs. In another study, place of residence was reported as an influential factor in perceiving supportive behaviors. It was stated that people living in suburban and rural areas had more unmet support needs [44], which is consistent with our study results showing that living in suburban areas is an influential factor.

Limitations

This study used self-report scales to gather data, which can be considered a limitation of the study. Another limitation of this study was the difficulty of accessibility to participants due to the prevalence of COVID-19 and the accurate observance of health protocols for participants' safety.

Conclusions

The findings of this study demonstrated that women perceive their spouses' behaviors as less supportive than their husbands' perceive women's behavior. This is consistent with other studies conducted in other parts of the world showing women with breast cancer find their husbands' behaviors less supportive. Our findings suggest the need for husbands to be more attentive to their behavior's impact on their wives and talking with each other about problems is the most imperative factor for couples to perceive support. Accordingly, it can be stated that couples who are reluctant to talk to each other about problems perceive less mutual support. Therefore, along with medications, medical consultation, and mentioned treatments, policymakers and managers should also focus on other types of interventions, including psychological consultation, in order to remove the psychological pressures of the disease from families and help couples to provide better support to each other.

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Conflict of interest

The authors have declared no conflicts of interest.

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VIA MEDICA

REVIEW ARTICLE

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Lung cancer among women — identifying risk factors

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ABSTRACT

The number of lung cancer cases estimates globally 2 million according to WHO, which represents approximately 11.6% of all cancers. The problem of lung diseases among women and women's lung cancer is relatively not often discussed in the literature. There is evidence that there is a different distribution of histological types between sexes. The prevalence of adenocarcinoma (ADC) among women is observed for many years with an increasing tendency. This review focuses on the lung cancer risk factors such as tobacco smoking, second-hand smoke exposure, genetic and environmental factors, comorbidities and infectious agents. The declining tendency in smoking points to the necessity of focusing on other risk factors. Analysis of them within the context of morbidity and mortality can help to develop more effective screening programs.

Key words: lung cancer, women, smoking, adenocarcinoma, risk factors

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Introduction

The number of lung cases estimates at 2 million according to WHO, which represents approximately 11.6% of all cancers. Global statistics concerning women show 725 thousand new cases and 576 thousand deaths due to that reason in 2018. The highest female age-standardised rate per 100,000 is observed in Hungary, Denmark, Netherlands (41.4–32.7) [1, 2]. In Poland, 7747 new cases among women were reported in 2017. Unfortunately, the number of deaths per year was higher — 7825 [3]. The 5-year life expectancy of patients with lung cancer is estimated at 13.5% [4].

Large analysis relating global patterns and temporal trends in incidence and mortality of lung cancer based on data from high-quality cancer registries was conducted by Wong et al. The conclusions revealed increasing trends of incidence among women in 19 countries, one with decreasing incidence, and 18 countries with stable incidence out of 38 countries. There were 16 countries with increasing mortality trends, 6 countries with decreasing trends and 14 countries with stable trends among women out of 36 countries [5]. The ageing of the female population born after World War II and their high tobacco consumption, improvement of health care of chronic diseases can partly explain that appearance.

There is evidence that there is a different distribution of histological types between sex. The prevalence of adenocarcinoma (ADC) among women is observed for many years with an increasing tendency. In one large study, the data concerning the epidemiology of ADC are presented based on cancer registry (Cancer Incidence in Five Countries, CI5) in the years 1998–2002 [6]. An increase of age-adjusted incidence of ADC among women was observed in all countries; in some countries, it was as high as twofold. The mean proportion of ADC of all lung cancer histological subtypes was higher among women than among men (45 *vs.* 34%, respectively).

The influence of sex is also the subject of study in lung cancer treatment. The goal of the Swedish nationwide cohort was an analysis of the differences

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in prognosis after pulmonary resection for lung cancer between men and women. The results show that women who underwent pulmonary resections for lung cancer had a significantly better prognosis than men [7]. The progress of new systemic therapies: molecular guided and immune-based therapy contributed to the improvement of survival in NSCLC. The benefit seems to be better among women than in men: 2-years survival improved from 26 to 35% in men and from 35 to 44% among women in the US from 2001 to 2016 [8].

The problem of lung diseases among women and women's lung cancer is relatively not often discussed in the literature and has not been embedded in clinical practice. Current aspects of lung cancer among women including the latest topics for research and the evidence on the specificity of female lung cancer were summarized in the authors' previous review [9]. This review focuses on the risk factors which are special for this serious disease among women. Some aspects of this problem are well documented, some of them appear in the minds of researchers. The authors believe that this overview will enrich the clinical practice of oncologists.

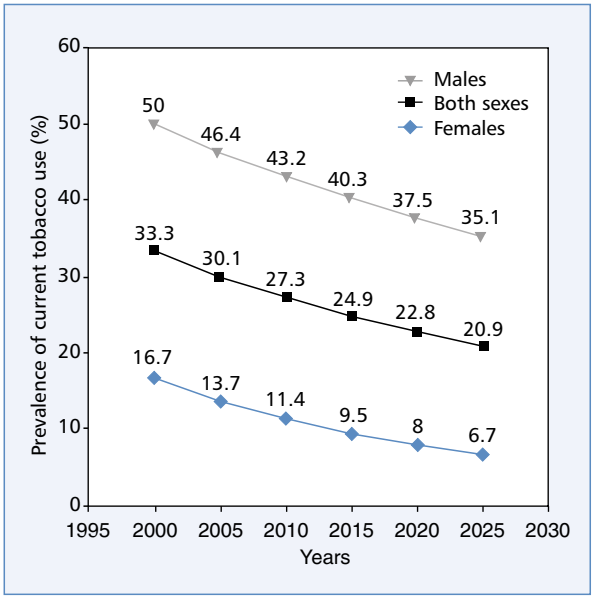

Figure 1. Global trends in the prevalence of tobacco use by sex based on World Health Organization [11]

Tobacco smoking

There is no doubt that smoking remains the main factor that causes lung cancer [10]. Tar which is formed after removing nicotine and water from cigarette smoke consists of about 3500 different compounds and most of them are carcinogenic [11].

There is a widespread opinion that lung cancer incidence is higher among smoking men than women and never-smoking women than men. The higher susceptibility by women to tobacco smoke was postulated. Whereas the large epidemiological studies did not confirm this view and only a nonsignificant tendency supporting it was shown [12, 13]. Even reverse relationships have been found in the large observation in the United States population the age-standardized lung cancer death rates among never-smoking men was 17.1/100 000 *vs.* 14.7/100 000 in women [14]. It should be pointed that it concerns one country, and it was race dependent.

Fortunately, the latest global trends estimated by WHO points out that the rates of prevalence of current tobacco use are declining (Fig. 1). The total number of smoking women is predicted to be reduced to 212 million by 2025 [15]. This reduction is observed in all world regions being slowest in European countries. However, cigarette smoke remains a "legally available consumer product which kills people". The increase in the number of tobacco smoke victims is highest in developing countries. Cigarette consumption is still very high among women in these countries with the prevalence of young women [15]. Recently, two-thirds of smokers are citizens of 10 countries, among them: Indonesia, Bangladesh, Turkey.

Unfortunately, Poland is a country with high tobacco consumption. Thus, the Polish data is presented. The estimated current tobacco smoking prevalence (age-standardised rate) in Polish females is 21.6% (*vs.* 30.3% in men) and it also shows declining trends over the last eleven years [16]. The most recent Polish representative survey reporting the prevalence of smoking (from 2019) reveals that the highest prevalence of smoking was observed among women aged 30–39 years. It is noticeable that divorced women smoked more often than married, single or widowed. Women smoked the most in cities between 20,000–500,000 citizens. They choose mainly regular cigarettes and hand-rolled tobacco products. Heated tobacco products and smokeless tobacco use are not popular in Polish women (2.1% and 0.6%, respectively) [17].

Considering the influence of e-cigarettes on the lung a few toxicological studies were conducted. The results pay attention to their adverse effects like cytotoxicity, oxidative stress and inflammatory response, reduction of the features of obturation in pulmonary function tests (FEV1/FVC) and a fraction of exhaled nitric oxide (FENO). The authors warn about the lack of studies involving the long-term health impact of these products [18]. It should be highlighted that the carcinogenic effect of classic cigarettes is incomparably higher than these products.

ETS exposure

Monitoring decreasing global tendency of smoking habit and taking into consideration diagnosis of lung cancer in never-smokers (10–15% of all cases) [19] one should focus on finding other risks factors of lung cancer. The problem, which is much more predominant among women than in men is second-hand smoke exposure (environmental tobacco smoke, ETS). In 2004 Oberg and at. conducted analysis of data from 192 countries which estimates that 35% of non-smoking females were exposed to second-hand smoke what had resulted in death from ischaemic heart disease, lower respiratory infections, asthma, and lung cancer. In total 603,000 deaths were attributable to second-hand smoke and lung cancer was a cause of 21,400 deaths. More deaths from second-hand smoke occurred among women (47%, compared to 26% in men) in this cohort [20]. It gives the reason for concerning the necessity of implementation of careful asking females about second-hand smoke exposure in medical anamneses and considering the participation of them in screening programs.

Genetic risk factors

Wakelee et al. [12] conducted a review based on the large, population-based cohorts which revealed that age-adjusted incidence rates of lung cancer among never-smokers aged 40 to 79 years ranged from 14.4 to 20.8 among women and 4.8 to 13.7 in men (per 100,000 person-years) what indicate that women are more likely than men to have lung cancer without smoking history and that genetic factors may be responsible for this fact. The primary characteristics of never-smokers compared to tobacco smokers with lung cancer are female sex, ADC histology and East Asian ethnicity [21–23].

The development of molecular pathology leads to precision diagnosis for lung cancer with recognition of molecular alterations which are the basis for targeted therapies [24]. Epidermal growth factor receptor (EGFR) and KRAS activating mutations are the most common in ADC. The proportion of molecular alterations incidence depends on smoking history, ethnicity and sex [25]. *EGFR* mutation occurs in the Asian population more often than in the Western population (47.9% *vs.* 19.2%) [26], and more often in non-smokers (43% *vs.* 11% in smokers) [27]. *EGFR* mutation is observed among Asian women even up to 60% [28]. In general, the most frequently observed mutated gene is p53. The prevalence of *KRAS* mutations is estimated at 15–30% [29]. Different genetic alterations are depending on the histopathologic type of lung cancer. The most frequently mutated genes in ADC are *KRAS*, *EGFR*, *MLL3*, and *STK11*; whereas in squamous cell carcinomas, there are PI3KCA, SOX2, CDK2, P63, FGFR1 and in small cell lung cancer: RB1, MLL2, SMO, and PI3KCA. Anticancer drug development has been made possible by anti-EGFR and anti-ALK/ROS1 therapeutics (tyrosine kinase inhibitors, TKIs) which play a critical role in the treatment of a selected group of patients [30, 31]. The greater benefit of TKIs is observed among women than in men.

When investigating the subject of genetic reasons of lung cancer, one cannot ignore genome-wide association studies that showed that variations at 5p15.33, 6p21.33, and 15q25.1, 9p21.3 can influence the risk of cancer in European populations [11, 32].

In a study from 2020, Xuemei Ji et al. [33] suggest KIAA0930 as a novel candidate gene for lung cancer risk (located at 22q13.31).

Other individual factors

A systematic review was performed to check if family history of lung cancer influences lung cancer risk. The results based on twenty-eight publications revealed that lung cancer risk of the probands' first-degree relatives was 1.88 times higher than that of their controls [34]. However, a family history of lung cancer was not associated with the female sex in the *EGFR* mutated cohort in the Gaughan et al. study [35].

Recently an interesting report showed two cases of paediatric lung cancers that probably developed through mother-to-infant transmission of cervical carcinoma. The authors assume that tumours arose from mother-to-infant vaginal transmission through aspiration of tumour-contaminated vaginal fluids during birth. They observed a similarity of the gene profiles of the tumour samples from the mothers and children [36].

The role of oestrogens in lung cancer development and progression is well established [37, 38] and previously described by the authors in details [9]. Briefly: oestrogen receptors are identified in lung tissue, cancer tissue and the cells which form tumour environment [39]. Thus, lung cancer development is modified by oestrogens from outside as well as produced locally. Aromatase (ARO) extensively expressed in NSCLC contributes to local oestrogen production. All the above data support hormonal influence on lung cancer among women with some therapeutic implications [40]. Female sex could be a factor considered as that, which influence lung carcinogenesis.

Environmental factors

The harmfulness of the environment also applies to lung cancer. An important risk factor for lung cancer among women is using solid fuels (coal, biomass,

and mixed fuels) for in-home cooking or heating. It is noticed mainly in developing countries. A meta-analysis that included studies from Asia, the USA, South America and Europe estimates that the risk of lung cancer among users of solid fuels is 70% higher than non-users [41].

Air pollution and precisely exposure to particulate matter (PM) in outdoor air pollution with aerodynamic diameter ≤ 2.5 μm or fine particles ($PM_{2.5}$) and particles ≤ 10 μm or inhalable particles (PM_{10}) has an association with the risk of lung cancer [42, 43]. World Health Organization declares diesel engine exhaust as a carcinogen based on evidence of a link with lung cancer [44, 45]. What is more, scientists consider gaseous pollutants, such as sulphur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and nitrogen dioxide (NO_2) as potential risk factor. However, results in that topic from previous studies seem to be inconsistent [46, 47]. Occupational carcinogens are well known for years and, what is interesting, a recently published systematic review confirms the increasing role of these risk factors [48]. According to the Global Health Data Exchange, the following agents relate to the death of cancer: arsenic, asbestos, benzene, beryllium, cadmium, chromium, diesel engine exhaust, formaldehyde, nickel, polycyclic aromatic hydrocarbons, silica, sulfuric acid, and trichloroethylene. Most of them relate to lung cancer and the risk for death after exposure to occupational agents increases in both sexes. One of the serious carcinogens is naturally occurring radon, which is considered as a second lung cancer risk factor after smoking. The large analysis of the studies conducted in never-smokers confirmed the relationship between residual radon and lung cancer, which was higher in never than in ever smokers and among man than women [49]. However, the synergistic effect of radon with smoking was pointed in this review leading to the conclusion, that, for both sexes, people living in the radon-prone area (> 100 Bq/m^3) should be considered as a high-risk group.

Knowing a passion for dieting among women it is worth to also approach some information about it. In an updated comprehensive literature review based on 58 articles, Fakhri et al. summarized information about diet and its potential influence on lung cancer. A higher risk of lung cancer could be linked to red meat, processed meat, and foods high in total or saturated fats [50]. Some observations present the protective effect on lung parenchyma of some items in the diets like fruits, vegetables, fish, nuts, soy, B vitamins, vitamin D, vitamin E, vitamin C, and zinc. However, US Preventive Services Task Force (USPSTF) concluded that there is still insufficient evidence to recommend any vitamins, minerals, and multivitamin supplementation for lung cancer prevention [25, 51].

Comorbidities

The well-known factors for lung cancer are also chronic pulmonary diseases like chronic obstructive pulmonary disease (COPD) and fibrotic lung diseases. The women who reported COPD were 1.64 times more likely to develop lung cancer than those who reported no history of COPD in a recent analysis, after adjusting for smoking status and intensity, ethnicity, education, BMI and income. The other results show that the associations between COPD and lung cancer were similar across subtypes after adjusting for smoking status and intensity [52]. Numerous clinical problems may occur due to the similarity of the clinical picture of lung cancer and COPD and because of that sometimes a proper diagnosis and appropriate treatment are implemented with delay [53]. Women seem to have a different clinico-radiological phenotype of COPD than men [54]. There is evidence that women produce less sputum than men despite this, they are more likely to have a chronic bronchitic phenotype [55]. However, the results of the study conducted by Kiri et al. [56] showed that COPD increased 3-year mortality in patients with NSCLC regardless of patient age or sex (higher mortality rates was observed above all in patients aged > 65 years). On the other hand in another study, no significant differences in overall survival between COPD and non-COPD patients with lung cancer have been noticed [57].

The association between lung cancer and interstitial lung disease (ILD) can be partly explained by the history of smoking and physiopathology of fibrogenesis and cancerogenesis. The relative risk of lung cancer is estimated to be 3.5- to 7.3-times higher in patients with ILD and lung cancer is diagnosed among them at 10–20% [58]. The association between ILD and lung cancer among women compering to men need more detailed investigation.

Infectious agents

The role of inflammation in favouring carcinogenesis is well known and the pathomechanisms of immune response in lung cancer are widely investigated in the last years [24]. However, it is difficult to present the differences between sex in these processes. Only the results of immunotherapy were found to be better or worse among women depending on the study [9]. Thus, one aspect of inflammation connected with infections is presented. Considering infectious risk factors of lung cancer in females one cannot ignore the influence of viral infections in particular human papillomavirus (HPV) and HIV. In various studies, the presence of oncogenic HPV DNA (type 16 and 18) in lung tumour tissues was

identified [59]. In an international pooled analysis HPV was found to be present more likely in lung cancer tissue than normal lung [60]. The meta-analysis conducted by Zhai K et al. indicated that lung with HPV infection has a strong association with lung cancer. Principally, HPV 16 and 18 infections significantly increase the risk of lung squamous cell carcinoma [61]. This may lead to reflect on a special screening for lung cancer in women with HPV infection.

Non-AIDS defining cancers (NADC) are an important cause of morbidity and mortality in HIV-positive individuals. NADCs of the lung are mostly comprised of non-small cell lung cancer (NSCLC), followed by small cell lung cancer (SCLC). The incidence of lung cancer in HIV-infected persons estimates 80–170 cases per 100,000 person-years [62, 63]. The hypothesis for association between lung cancer and HIV infection refers to chronic pulmonary inflammation connected with infections contributes to carcinogenesis [64]. The role of HIV infection alone was also investigated. The results are inconclusive. Sigel et al. [56] indicated that HIV was an independent risk factor for lung cancer after controlling for potential confounders including smoking. On the other hand, Hessol et al. [65] showed that HIV infection alone was not an independent risk factor for lung cancer but that the amount of cigarette smoking and prior AIDS pneumonia were major factors for the development of lung cancer among HIV-infected patients.

COVID-19 infection involving currently according to WHO more than 100 million confirmed cases and causing more than 2 million death globally is a new factor which causes the acute respiratory disorder. There are some clinical findings in COVID-19 patients which are also reported to be high-risk findings associated with lung cancer development. However, the speculations about the impact of COVID-19 on lung cancer risk seem to be premature

The ground-glass opacity (GGO) (widespread among COVID-19 patients) is a frequent radiological finding in a patient with lung cancer [66, 67]. The strategy for GGO in lung cancer screening is the subject of international discussions and regulations. There may be a need for follow up in the patients with persistent GGO after SARCov-2 infection for early detection of the pre-neoplastic lesions [68]. Another common aspect of COVID-19 infection and lung cancer are disturbances in the immune system. In the blood of COVID-19 infected patients the concentration of IL-6, IFNγ, MCP1, and IP-10 were found to be elevated during COVID-19 [69, 70]. These cytokines are involved in invasion, metastasis, and epithelial-mesenchymal transition in lung cancer. An interesting current result of meta-analysis including 3,111,714 globally reported cases of confirmed COVID-19 patients showed that there is no difference

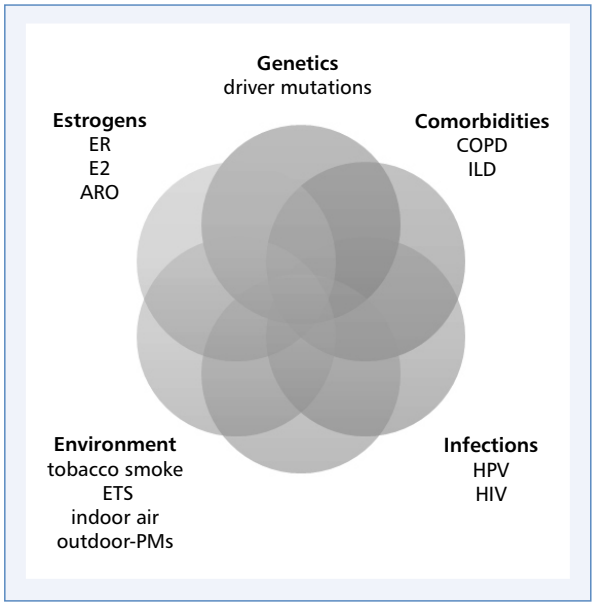

Figure 2. Possible and documented risk factors for lung cancer among women; ARO — aromatase; ER — oestrogen receptor; E2 — 17-β-oestradiol; ETS — environmental tobacco smoke; COPD — chronic obstructive lung disease; HPV — human papillomavirus; HIV — human immunodeficiency virus; ILD — interstitial lung diseases; PMs — particular matters

in the proportion of infection between males and females, however, men have almost three times the odds of requiring intensive treatment unit admission and higher odds of death compared to women. These results have highlighted the importance of considering sex as a variable in fundamental and clinical research and can help in the clinical management of COVID-19 [71]. The new global problem which is COVID-19 needs further investigations.

Conclusion

Lung cancer, which has been associated with the male sex for years, has become a serious problem among women. The declining tendency in smoking induces focusing on other risk factors. An analysis of current risk factors within the context of morbidity and mortality can help to develop effective screening programs. The most important risk factors which need intensive investigations for lung cancer in women are summarized in Figure 2.

Conflict of interest

The authors have declared no conflicts of interest.

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VIA MEDICA

CASE REPORT

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Recurrent Her-2 positive occult breast cancer presenting with zosteriform cutaneous metastases: a case report

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ABSTRACT

Various cutaneous metastasis patterns are described in breast cancer. Zosteriform metastases are rare cutaneous metastases, which appear in a dermatomal distribution. A 66-year woman presented with a 1-month history of nodular lesions on the left posterior hemithorax area. Biopsy was reported as human epidermal growth factor receptor (Her) 2 positive, hormone receptor-negative breast carcinoma metastasis. Dual blockade therapy targeting Her-2 overexpression was initiated for the patient. Treatment response was obtained after 3 cycles. There was a significant improvement in skin lesions. Zosteriform cutaneous metastases can be the early sign of systemic spread and can show an initial response to therapy. Therefore, physicians should perform an exhaustive physical examination including that of skin.

Key words: zosteriform, cutaneous metastases, recurrent, occult, breast cancer

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Introduction

Cutaneous metastases of solid malignancy are relatively uncommon, with an incidence ranging from 0.7 to 10.4% [1]. The incidence of breast carcinoma cutaneous metastases is 23.9% [2]. Most of the cutaneous metastases appear as adjacent lesions concerning the breast primary. Various cutaneous metastasis patterns such as zosteriform, ulcers, erysipelas, tinea infections, erythema annulare are described, a nodular pattern is the most common presentation [3]. The sites of cutaneous metastases are the abdomen and chest wall (most common), head/neck region, and extremities. Breast cancer tends to metastasize less frequently to the lower abdomen, back, and upper arms; and unusual to the perianal region, buttocks, eyelids, and lower extremities [4]. Solid cancers' skin metastases are related to the advanced stage of cancer, whereas breast cancers' cutaneous metastases can appear in locally advanced disease [5]. In one study, it was found that skin metastasis emerged as the initial finding in 12% of breast cancer patients [6]. However, data on the frequency of presentation with skin metastases in patients with recurrent breast cancer are limited.

Diffuse skin metastases without distant spread occur in human epidermal growth factor receptor (Her) 2-amplified disease [6]. Uncommonly, cutaneous metastases can be a sign of cancer recurrence. Often, the period from the initial diagnosis to cutaneous metastasis is 5 years [7]. Zosteriform metastases are rare cutaneous metastases, which appear in a dermatomal distribution [8]. This research aims to present a case of recurrent Her-2 positive breast cancer who presented with zosteriform skin metastases 7 years later.

Case presentation

A 66-year woman presented with a 1-month history of nodular lesions on the left posterior hemithorax area. In medical history, she had left mastectomy after neo-

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adjuvant chemotherapy for breast cancer 7 years ago. Family history was unremarkable. Vital findings were stable. On physical examination, there were pink-red and black raised skin bumps that were distributed along a single dermatome in the posterior of the left hemithorax (Fig. 1). There was no left breast tissue, there was an approximately 20 cm incision line in this area. CA 15.3 was 12.6 U/mL (0–35) and there was no abnormal value in other laboratory levels. Biopsy was taken from these lesions. The result was reported as Her-2 positive, hormone receptor-negative breast carcinoma metastasis. Positron Emission Tomography-Computed Tomography (PET-BT) findings are as follows: left breast was not observed, there was no mass in the right breast. There were expansive skin lesions of 17 × 11 mm (SUV max: 5.77) in the left posterolateral hemithorax and 8 × 5 mm (SUV max: 3.48) in the medial. Brain magnetic resonance imaging was performed, and no lesions were detected. Although there is no mass in the patient's right breast, according to the patient's history of breast cancer and the biopsy result, occult breast cancer was diagnosed. Skin lesions were evaluated as zosteriform cutaneous metastasis. Echocardiography was performed before treatment and the ejection fraction was 60%. Dual blockade therapy targeting Her-2 overexpression was initiated for the patient. Trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance dose, every 3 weeks), pertuzumab (840 mg loading dose, 420 mg maintenance dose, every 3 weeks), and docetaxel (75 mg/m^2, every 3 weeks) were initiated. Treatment response was obtained after 3 cycles. There was a significant improvement in skin lesions (Fig. 2). After 6 cycles were completed, maintenance treatment was started with trastuzumab (6 mg/kg, every 3 weeks) and pertuzumab (420 mg, every 3 weeks). The patient was observed with no evidence of progressive disease.

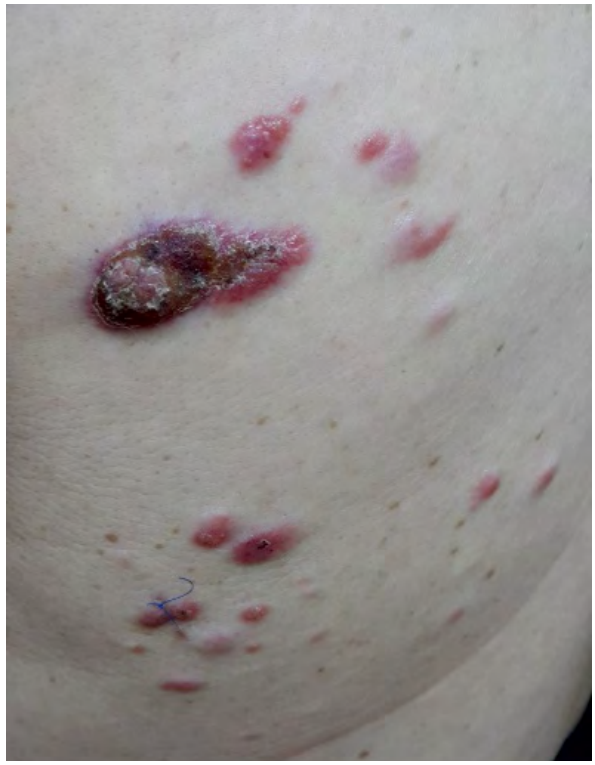

Figure 1. Presentation of recurrent breast cancer with zosteriform cutaneous metastases

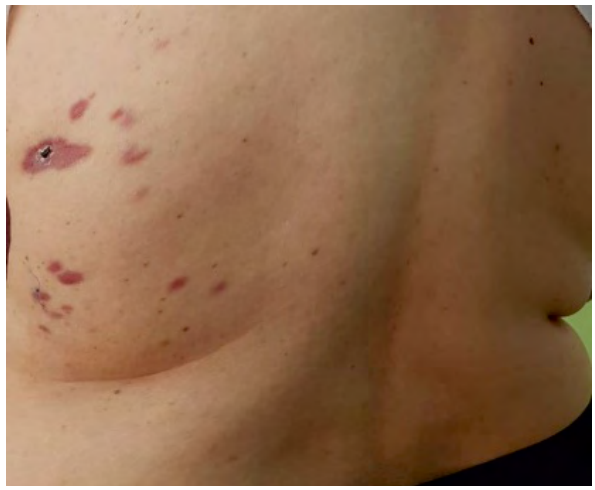

Figure 2. Regression of treatment-related zosteriform cutaneous metastases

Discussion

Cutaneous metastases though rare can be the first sign of cancer recurrence. Zosteriform metastases are rare cutaneous metastases, which appear in a dermatomal distribution. This case presented with zosteriform cutaneous metastasis in the back from Her-2 positive breast cancer occurring after 7 years later adjuvant anthracycline-based regimen plus trastuzumab therapy. Most of the cutaneous metastases occur as direct lesions in relation to the breast primary. Zosteriform cutaneous metastases may rarely be in the form of distant metastases in the back, as in this case presented. The mechanism of zosteriform distribution is unknown. Koebnerization at the site of previous zoster infection and neural spread through the dorsal ganglia are theories in the pathophysiology of zosteriform metastasis [9]. The skin does not appear to be the target organ for metastasis development. Cutaneous metastasis is a rare clinical sign. Usually, the development of skin metastases is poorly prognostic [10]. Cutaneous metastases result from hematogenous, lymphatic, or contiguous dissemination [10]. A review of the literature demonstrated

that the incidence of cutaneous metastasis ranges from 0.7% to 10% [1]. Cutaneous metastases may present different appearances in breast cancer. The most common form is the nodule pattern and is seen in the chest wall and abdomen. The sizes of these nodules vary between 1 and 3 cm. and appear as single or multiple hardened lesions located on the dermis and subcutaneous tissue.

Several cases of cutaneous metastases after or during treatment have been defined in the literature [11, 12]. Herein a case is described in which a patient with Her-2-positive metastatic breast cancer had zosteriform cutaneous progression 7 years later treatment. To the authors' knowledge, there was no such case in the literature. In brain metastases, the effectiveness of monoclonal antibodies is generally limited due to the brain-blood barrier or to the so-called "immune privilege" of the brain [13, 14]. Interestingly, immune privilege has been defined also in the skin [15]. It has been claimed that tumour cells are a sanctuary-like region in the cutaneous microenvironment [16].

Zosteriform metastases are a rare clinical presentation of cutaneous metastases and can be the early sign of systemic spread. Zosteriform cutaneous metastases can show an initial response to therapy. Therefore, physicians should perform an exhaustive physical examination including that of skin.

Conflict of interest

The authors have declared no conflicts of interest.

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VIA MEDICA

CASE REPORT

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Development of second primary multiple myeloma five years after treatment for limited-stage small cell lung cancer: a rare case report

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ABSTRACT

Introduction. The development of a second primary malignancy (SPM) following small cell lung cancer (SCLC) has been previously reported in the literature. Especially smoking-related malignancy coupling is well known. The development of multiple myeloma (MM) in long-term survivors after treatment for SCLC is unknown. Here, we report the first case in the literature who developed MM 5 years after treatment for limited-stage SCLC.

Case report. A 67-year-old male patient was diagnosed with limited-stage SCLC. After he received chemotherapy and radiotherapy, he was followed up without medication. He was admitted to the hospital with back pain and dyspnea 5 years after the diagnosis of small cell lung cancer. MRI revealed osteolytic lesions in the vertebrae. Laboratory testing revealed a markedly elevated serum IgA and an elevated serum beta-2 microglobulin level. Serum immunofixation revealed IgA lambda-type M-protein. Lambda excretion in urine immunofixation electrophoresis was observed. Bone marrow aspiration revealed the frequency of plasma cells to be 80% of all nucleated cells. Hence, the final diagnosis revealed IgA lambda free light chain MM. Treatment was given for multiple myeloma. In the follow-up, the patient experienced increased dyspnea and developed bilateral pleural effusion. The cytology sent from thoracentesis sampling was reported as plasmocyte-rich material. The patient fell into a coma and died in an intensive care unit.

Conclusion. We presented the development of MM 5 years after treatment in a patient with SCLC who were treated for one year and then followed up with stable findings. It should be kept in mind that a patient with SCLC who is a long-term survivor and presents with back pain may have developed a primary malignancy originating from bone marrow rather than a bone metastasis. Patients should be advised smoking cessation after the treatment and diagnosis of SCLC. Also, the patients with SCLC who are long-term survivors should be closely monitored for the development of SPM.

Key words: small cell lung cancer, multiple myeloma, second primary malignancy

Oncol Clin Pract 2021; 17, 5: 232–235

Introduction

Small cell lung cancer (SCLC) is a high-grade neuroendocrine tumor that represents about 15 percent of all lung cancers. Nearly all patients with SCLC are current or former smokers [1]. Multiple myeloma (MM) is a hematologic malignancy characterized by the infiltration of bone and bone marrow with neoplastic plasma cells and the extensive presence of monoclonal Ig or light chains in serum or urine [2]. Second primary

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malignancy (SPM) associated with smoking was found to be high in patients with lung cancer. The concomitance of a malignancy originating from plasma cells such as multiple myeloma and SCLC has not been described in the literature. In this case report, we present the development of multiple myeloma following SCLC treatment.

Case presentation

A 67-year-old male patient was diagnosed with limited-stage SCLC in January 2012, proven by thoracic and abdomino-pelvic computed tomography (CT) scan and right supraclavicular lymphadenopathy biopsy. The patient had no history of other medical comorbidities. The patient had a smoking history of 48 pack-years until the moment of diagnosis. He was treated with four cycles of cisplatin + etoposide combination chemotherapy (cisplatin 80 mg/m^2 intravenous (iv) infusion on D1, etoposide 100 mg/m^2 iv infusion on D1–3, repeated every 3 weeks) along with concurrent thoracic radiotherapy. In July 2012, he was treated for nine weeks of weekly topotecan (4 mg/m^2 iv infusion on D1, D8 and D15, repeated every 28 days) followed by six cycles of cyclophosphamide+doxorubicin+vincristin (cyclophosphamide 1000 mg/m^2 iv infusion on D1, doxorubicin 40 mg/m^2 iv infusion on D1, vincristine 1 mg/m2 iv infusion on D1, repeated every 3 weeks) chemotherapy due to progression of lesions in the lung. After treatment, the lymph nodes in the cervical region disappeared, and the soft tissue mass in the right paratracheal area was markedly regressed in comparison with previous imaging. With these findings, the patient was monitored without drug treatment. There was no cigarette use during the one year when the patient received chemotherapy. However, he started to smoke again six months after the end of the treatment (one pack of cigarettes a day. In the last follow-up imaging performed in May 2017, the findings of stable disease were persisted. He was admitted to the Medical Oncology Department with back pain and dyspnea in August 2017. He had back pain for about two months and did not respond to painkillers. The physical examination revealed diffuse rhonchus in both lungs. Other vital signs and the physical examination were normal. Laboratory tests performed are displayed in Table 1. Bone marrow biopsy, serum protein electrophoresis and thoracic and lumbar magnetic resonance imaging (MRI) were done to rule out metastatic deposits in the patient and to know the cause of pancytopenia, hypercalcemia and elevated erythrocyte sedimentation rate (ESR). MRI revealed osteolytic lesions in the vertebrae (Fig. 1). Laboratory testing revealed a markedly elevated serum immunoglobulin (Ig) A (IgA) level (59.3 g/L, reference range: 0.7–4 g/L) and an elevated serum beta-2 microglobulin level (5.33 mg/L, reference range: 0.97–2.64 mg/L) (Tab. 2). Serum immunofixation revealed IgA lambda-type M-protein. Lambda excretion in urine immunofixation electrophoresis was observed. Bone marrow aspiration revealed the frequency of plasma cells to be 80% of all nucleated cells. Microscopic examination and flow cytometric analysis of bone marrow aspirate revealed

Table 1. Serum laboratory levels and protein electrophoresis

Parameter	Level	Normal range
WBCc	3.6 × 10^3/uL	(4–10)
Neu	1.86 × 10^3/uL	(1.5–7.3)
Hb	8,5 g/dL	(12.1–17.2)
Plt	97 × 10^3/uL	(150–400)
Sedimentation rate	> 140 mm/hour	(0–20)
Ure	31 mg/dL	(15–44)
Cre	1.17 mg/dL	(0.72–1.25)
Na	142 mmol/L	(136–145)
K	4.8 mmol/L	(3.5–5.1)
Ca	11.47 mg/dL	(8.4–10.2)
Total protein	7.8 mmol/L	(3.5–5.1)
Albumin	2.2 g/dL	(3.5–5)
The rates of protein electrophoresis		
ALBUMIN	31.11%	(55.8–65)
ALFA1	4.37%	(2.2–4.6)
ALFA2	8.08%	(8.2–12.5)
BETA	22.40%	(7.2–14.2)
GAMA	34.04%	(11.5–18.6)

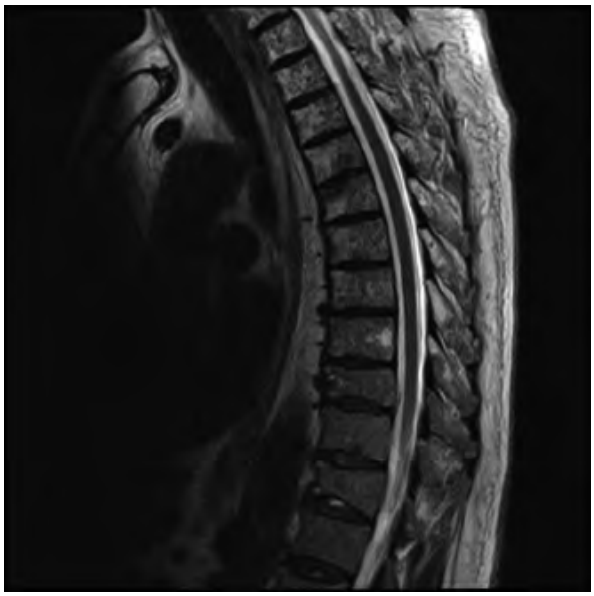

Figure 1. Sagittal magnetic resonance imaging with multiple bone osteolytic lesions of the cervical and thoracic spine

Table 2. Serum immunoglobulin levels

Parameter	Level	Normal range
Immunoglobulin G	1.53 g/L	(7–16)
Immunoglobulin A	59.3 g/L	(0.7–4)
Immunoglobulin M	0.186 g/L	(0.4–2.3)
Lambda free light chain	62.2 mg/dL	(8.3–27)
Kappa free light chain	9.29 mg/dL	(6.7–22.4)
Free kappa to free lambda ratio	0.15	(0.26–1,65)
Beta 2 microglobulin	5.33 mg/L	(0.97–2.64)

elevated numbers of CD38-positive abnormal plasma cells. In the bone marrow FISH analysis, 13q14.3 80% normal 20% number 13 chromosomal monosomy signals were observed, 25% CKS1B gene expression was increased. Also, p53 and Ig heavy chain (IgH)/ /breakapart were normal. Hence, the final diagnosis revealed IgA lambda free light chain MM. The patient was transferred to the hematology clinic and was treated with zoledronic acid (4 mg iv infusion) and one cycle of bortezomib plus cyclophosphamide plus dexamethasone (bortezomib 1.5 mg/m^2 subcutaneously on D1, 8, 15, 22, cyclophosphamide 300 mg/m^2 orally on D1, 8, 15, 22, dexamethasone 40 mg orally on D1, 18, 15, 22, repeated every 28 days) combination chemotherapy. In the follow-up, the patient experienced increased dyspnea and developed bilateral pleural effusion. The cytology sent from thoracentesis sampling was reported as plasmocyte rich material. The patient was admitted to the intensive care unit because of severe respiratory distress. The patient fell into a coma and died on the 3rd day of admission to an intensive care unit.

Discussion

SCLC is an aggressive form of lung cancer characterized by rapid doubling time and high growth rate and early metastasis development and is strongly associated with smoking. The most important prognostic factor in patients with SCLC is the extent of disease (stage) at presentation. Although SCLC is highly responsive to both chemotherapy and radiotherapy, it commonly relapses within months despite treatment. For patients with the limited-stage disease, limited to the ipsilateral hemithorax and regional lymph nodes, median survivals range from 15 to 20 months, and the reported five-year survival rate is 10 to 13 percent. Patients with the limited-stage disease are primarily treated with a combination of chemotherapy (cisplatin plus etoposide) and radiation therapy. SCLC has been rare in never smokers. Exposure to tobacco and multiple genetic defects including p53 mutations, loss of the retinoblastoma gene (RB1) function at 13q14, loss of PTEN, MYC amplification, activation of telomerase, and strong expression of cKit are related with oncogenesis in SCLC. However, mutations in the EGFR and KRAS oncogenes and p16 abnormalities are rare [3, 4].

MM is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. Older age, immunosuppression, environmental exposures such as radiation, benzene, and other organic solvents including herbicides, and insecticides, and some primary (IgH chain translocations, trisomies) and secondary cytogenetic abnormalities (secondary IgH translocations, deletion of 17p13 on p53 locus, Ras mutations, activation of NF kappa B) appear to play a major role in the development of MM [5, 6].

Careful monitoring for the development of SPM in patients with SCLC is necessary for long-term survivors, because the risk of developing SPM in these patients is significantly increased. The cessation of cigarette smoking after successful therapy is associated with a significantly decreased risk of an SPM [7]. The risk of SPM was increased by a number of chemotherapy cycles > 6, an age of > 60, treatment with combination chemotherapy, and chest irradiation [8, 9]. In a study including sixty-one patients who survived for more than two years, SPM was observed in seven patients (four with non-small cell lung cancer, two with gastric cancer, and one with prostate cancer) [10]. In another study including forty-seven patients who were identified to be free of disease at two years, SPM was observed in 14 patients. In these patients, aerodigestive tract malignancies associated with smoking as SPM has been developed [11]. Also, in previous studies, the development of hematologic malignancy as SPM in long-term survivors after treatment for SCLC has been reported. Hematologic malignancy developed in these patients was leukemia [12–15]. However, MM development as SPM in patients with SCLC has never been reported. To the best of our knowledge, this is the first reported case in the literature. The patient stopped smoking during the treatment for SCLC, but had started again six months after the end of the treatment. From the literature and past experience, we were expecting smoking-induced SPM development, but we were surprised by the development of MM in our patient. Because MM is not a smoking-related malignancy. We think that increased predisposition to MM development may relate to secondary effects of multimodality treatment including chemotherapy and radiotherapy.

Conclusion

We presented the development of MM 5 years after treatment in a patient with SCLC who was treated for

one year and then followed up with stable findings. It should be kept in mind that a patient with SCLC who is a long-term survivor and presents with back pain may have developed a primary malignancy originating from bone marrow rather than a bone metastasis. Patients should be advised smoking cessation after the treatment and diagnosis of SCLC. Also, the patients with SCLC who are long-term survivors should be closely monitored for the development of SPM.

Clinical practice points

Patients with long-term remission after being treated for small cell lung cancer must be close followed up for second primary cancers.

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Conflict of interest

The authors have declared no conflicts of interest.

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