research article

Inquiry and computer program Onko-Online: 25 years of clinical registry for breast cancer at the University Medical Centre Maribor

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Background. High-quality routine care data collected in the clinical registry play a significant role in improving the management of cancer patients. Clinical cancer registries record important data in the course of cancer diagnosis, treatment, follow-up and survival. Analyses of such comprehensive data pool make it possible to improve the quality of patients care and compare with other health care providers.

Methods. The first inquiry at the Department of Gynaecologic and Breast Oncology of the then General Hospital Maribor to follow breast cancer patients has been introduced in 1994. Based on our experience and new approaches in breast cancer treatment, the context of inquiry has been changed and extended to the present form, which served as a model for developing a relevant computer programme named *Onko-Online* in 2014.

Results. During the 25-year period, we collected data from about 3,600 breast cancer patients. The computer program *Onko-Online* allowed for quick and reliable collection, processing and analysis of 167 different data of breast cancer patients including general information, medical history, diagnostics, treatment, and follow-up.

Conclusions. The clinical registry for breast cancer *Onko-Online* provides data that help us to improve diagnostics and treatment of breast cancer patients, organize the daily practice and to compare the results of our treatment to the national and international standards. A limitation of the registry is the potentially incomplete or incorrect data input by different healthcare providers, involved in the treatment of breast cancer patients.

Key words: clinical registry; computer program; breast cancer

Introduction

In Slovenia, we have one of the oldest population-based cancer registries in Europe named the Cancer Registry of Republic of Slovenia. It was founded at the Institute of Oncology in Ljubljana in 1950. This registry monitors the population burden for all malignant and non-malignant oncological diseases.[1] Clinical registers in Slovenia are needed for collecting additional information on certain cancers.[2] The Clinical Register of Skin Melanoma was founded in 2017 as the first special clinical registry for Slovenia.[3]

At our Department of Gynaecologic and Breast Oncology we introduced seven different inquiries for gynaecological (vulvar, vaginal, cervical, endometrial, ovarian, fallopian tube cancer) and breast cancer in 1994. For all of them, a computer program running in Microsoft Access has been designed and we published two articles on the use of this software for follow-up of patients with ovarian malignancies in 1996 and 1999.[4,5]

Methods

In the last decades, treatment of the most common female carcinoma, breast cancer, changed dramatically in terms of surgery and systemic

treatment. Regarding previous experience with collecting data of cancer patients and including relevant data, the context of the inquiry for breast cancer has been changed and extended to achieve the form, which we use nowadays. The updated inquiry served as a model for developing an adequate computer program named *Onko-Online* in 2014, which records data during diagnostics, treatment and follow-up.

The paper inquiry was completed during diagnostic and treatment procedures. Included in the program were all breast cancer patients at first presentation who started treatment at our institution irrespective of the disease stage. If a patient underwent diagnostic procedures at a different institution, it was possible to collect data based on medical records. Therefore, these patients were also included to the program in case their first treatment was initiated at our institution. General data were partly collected when the diagnosis of breast malignancy was established.

After completing primary treatment, data were recorded using the computer program *Onko-Online*, which allowed for processing and analysing of the obtained data. Hard copies were completed by the doctor in charge. The data from hard copies were put into the computer program by a clerk with adequate training.

The documentation was also kept in the form of printed copies as part of health records.

Results

The inquiry for breast cancer covered 167 different information, divided into 11 sections: general data (G), medical history (MH), clinical examination (CE), mammography (M), ultrasound (US), preoperative investigations (PI), surgery (S), radiotherapy (RT), histopathology (H), systemic treatment (ST), and follow-up (FU).

General data consisted of the identification data and data regarding treatment collected at the end of primary treatment (Figure 1).

The data were recorded using the computer program when patients completed their primary treat-

BREAST CANCER

G1 year/no.:

G2 NAME AND G3. FAMILY NAME: | **G4 GENDER:**

G5 PERSONAL IDENTIFICATION NUMBER: | **G6 AGE:**

G7 DATE OF BIRTH:

G8 CARD NO. OF CBD (BREAST DISEASE CENTER): | **G9 CARD NO. GIN:** | **PC NO.:**

G10 DATE OF LAST EXAMINATION (or EX): _____
(last check-up, field S1.)

G11 STATUS AT LAST FOLLOW-UP (or EX):
(last check-up, field S8.)

0 alive, no symptoms
1 alive, partial remission (PR)
2 alive, stable disease (SD)
3 alive, relapse
4 alive, progressive disease (PD)
5 alive, condition unknown
6 ex due to breast malignancy
7 ex during treatment
8 ex due to other disease, no breast cancer symptoms
9 ex due to other disease, breast cancer symptoms present
10 ex, cause unknown
11 condition unknown

G12 DG: _____ | **G13 DATE OF DG:** _____

1 DCIS	☐R	☐ L	6 mucinous carcinoma	☐R	☐ L
2 ductal carcinoma	☐R	☐ L	7 tubular carcinoma	☐R	☐ L
3 LCIS	☐R	☐ L		☐R	☐ L
4 lobular carcinoma	☐R	☐ L			
5 medullary carcinoma	☐R	☐ L	8 other (please, specify) _____		

G14 STAGE:

TX T0 TIS T1 *T1mi* *T1a* *T1b* *T1c* T2 T3 T4a T4b T4c T4d

NX N0 N1 N2 *N2a* *N2b* N3 *N3a* *N3b* *N3c*

MX M0 M1

G15 DIFFERENTIATION: 1 G1 2 G2 3 G3

G16 INTRINSIC TUMOR SUBTYPE: 1 luminal A 2 luminal B, HER2 negative 3 luminal B, HER2 positive 4 HER2 positive non-luminal 5 triple negative

G17 TREATMENT:

0 no		5 complete/full chemotherapy	9 hormone therapy
1 tumorectomy	☐R ☐ L	6 non-complete chemotherapy	10 other (please, specify)
2 mastectomy	☐ R ☐ L	7 non-adjuvant chemotherapy	
3 SNB	☐R ☐ L	8 beam radiation	
4 axillary clearance	☐R ☐ L		

G18 DATE OF 1st RELAPSE	**G21 DATE OF 2nd RELAPSE**	**G24 DATE of 3rd RELAPSE**	**G27 DATE of 4th RELAPSE**
_____	_____	_____	_____
G19 SITE OF 1st RELAPSE	**G22 SITE OF 2nd RELAPSE**	**G25 SITE of 3rd RELAPSE**	**G28 SITE of 4th RELAPSE**
1 bones 7 same breast	1 bones 7 same breast	1 bones 7 same breast	1 bones 7 same breast
2 axilla 8 other breast	2 axilla 8 other breast	2 axilla 8 other breast	2 axilla 8 other breast
3 lungs 9 soft tissues	3 lungs 9 soft tissues	3 lungs 9 soft tissues	3 lungs 9 soft tissues
4 liver 10 chest wall	4 liver 10 chest wall	4 liver 10 chest wall	4 liver 10 chest wall
5 brain 11 other	5 brain 11 other	5 brain 11 other	5 brain 11 other
6 local relapse	6 local relapse	6 local relapse	6 local relapse
G20 1st LINE TREATMENT	**G23 2nd LINE TREATMENT**	**G26 3rd LINE TREATMENT**	**G29 4th LINE TREATMENT**
0 no	0 no	0 no	0 no
1 surgical	1 surgical	1 surgical	1 surgical
2 systemic chemotherapy	2 systemic chemotherapy	2 systemic chemotherapy	2 systemic chemotherapy
3 systemic-targeted	3 systemic-targeted	3 systemic-targeted	3 systemic-targeted
4 systemic hormone therapy	4 systemic hormone therapy	4 systemic hormone therapy	4 systemic hormone therapy
5 beam radiation	5 beam radiation	5 beam radiation	5 beam radiation
6 other (please, specify)	6 other (please, specify)	6 other (please, specify)	6 other (please, specify)

FIGURE 1. General data.

MEDICAL HISTORY

MH1 FAMILY HISTORY
0 none
1 tuberculosis
2 diabetes
3 allergies
4 mental disorders
5 STDs
6 other (_____)

MH2 FAMILY HISTORY OF CANCER
0 none (go to A5)
1 breast
2 ovary
3 uterus
4 GIT
5 other (_____)

MH3 FAMILY RELATIONSHIP
1 mother
2 sister
3 other (_____)

MH4 AGE AT DISEASE ONSET (in years) (see A3)
1 _____
2 _____
3 _____

MH5 FIRST PERIOD (age in years)
_____

MH6 NUMBER OF PREGNANCIES
_____

MH7 NUMBER OF MISCARRIAGES
_____

MH8 NUMBER OF INDUCED ABORTIONS
_____

MH9 NUMBER OF DELIVERIES/BIRTHS
_____

MH13 AGE AT FIRST BIRTH (years)
_____

MH11 BREASTFEEDING
0 no (go to A13)
1 yes

MH12 TOTAL DURATION OF BREASTFEEDING
_____

MH13 HORMONAL CONTRACEPTION
0 never (go to A15)
1 before
2 now

MH14 NUMBER OF YEARS of OCP USE
_____

MH15 FERTILITY TREATMENT
0 no (go to A18)
1 yes

MH16 DURATION OF FERTILITY TREATMENT (months)
_____

MH17 NUMBER OF STIMULATED CYCLES
_____

MH18 MENOPAUSE
0 not yet (go to A20)
1 natural
2 artificial/triggered

MH13 AGE AT MENOPAUSE (years)
_____

MH20 HORMONE THERAPY (PERI- OR POSTMENOPAUSE)
0 never (go to A23)
1 estrogen
2 estrogen-progesterone
3 other (_____)

MH21 NUMBER OF YEARS of HRT USE
_____

MH22 NUMBER OF YEARS since DISCONTINUED HRT
_____

MH23 SMOKING
0 never (go to A25)
1 before
2 now

MH24 NUMBER OF PACKAGES-YEARS (number of years x no. of packages daily)
_____

MH25 ALCOHOL CONSUMPTION
0 never
1 moderate (< 20g [1 unit] per day)
2 excessive (> 20g per day)

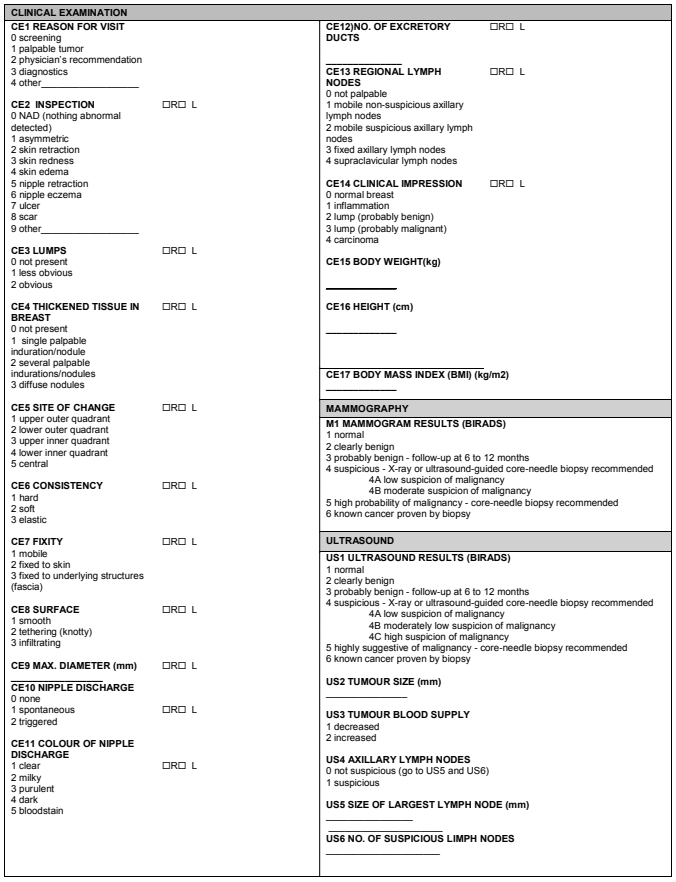
MH26 PREVIOUS OR PRESENT CONDITIONS
0 none
1 arterial hypertension
2 diabetes
3 obesity
4 coronary heart disease
5 other_____

MH27 PREVIOUS OR CURRENT CANCER DISEASES
0 none
1 other breast
2 ovary
3 GIT_____
4 other_____

MH28 SIGNS AND SYMPTOMS
0 none
1 palpable tumor
2 painful breast
3 skin changes
4 nipple discharge
5 palpable lymph nodes
6 pain in bones
7 abdominal pain
8 dyspnea
9 coughing
10 neurological symptoms
11 losing weight
12 other _____

MH29 DURATION OF SIGNS AND SYMPTOMS (in months)
_____

FIGURE 2. Medical history.



CLINICAL EXAMINATION

CE1 REASON FOR VISIT
0 screening
1 palpable tumor
2 physician's recommendation
3 diagnostics
4 other_____

CE2 INSPECTION ☐R☐ L
0 NAD (nothing abnormal detected)
1 asymmetric
2 skin retraction
3 skin redness
4 skin edema
5 nipple retraction
6 nipple eczema
7 ulcer
8 scar
9 other_____

CE3 LUMPS ☐R☐ L
0 not present
1 less obvious
2 obvious

CE4 THICKENED TISSUE IN BREAST ☐R☐ L
0 not present
1 single palpable induration/nodule
2 several palpable indurations/nodules
3 diffuse nodules

CE5 SITE OF CHANGE ☐R☐ L
1 upper outer quadrant
2 lower outer quadrant
3 upper inner quadrant
4 lower inner quadrant
5 central

CE6 CONSISTENCY ☐R☐ L
1 hard
2 soft
3 elastic

CE7 FIXITY ☐R☐ L
1 mobile
2 fixed to skin
3 fixed to underlying structures (fascia)

CE8 SURFACE ☐R☐ L
1 smooth
2 tethering (knotty)
3 infiltrating

CE9 MAX. DIAMETER (mm) ☐R☐ L
_____

CE10 NIPPLE DISCHARGE
0 none
1 spontaneous ☐R☐ L
2 triggered

CE11 COLOUR OF NIPPLE DISCHARGE
1 clear ☐R☐ L
2 milky
3 purulent
4 dark
5 bloodstain

CE12)NO. OF EXCRETORY DUCTS ☐R☐ L
_____

CE13 REGIONAL LYMPH NODES ☐R☐ L
0 not palpable
1 mobile non-suspicious axillary lymph nodes
2 mobile suspicious axillary lymph nodes
3 fixed axillary lymph nodes
4 supraclavicular lymph nodes

CE14 CLINICAL IMPRESSION ☐R☐ L
0 normal breast
1 inflammation
2 lump (probably benign)
3 lump (probably malignant)
4 carcinoma

CE15 BODY WEIGHT(kg)
_____

CE16 HEIGHT (cm)
_____

CE17 BODY MASS INDEX (BMI) (kg/m2)
_____

MAMMOGRAPHY

M1 MAMMOGRAM RESULTS (BIRADS)
1 normal
2 clearly benign
3 probably benign - follow-up at 6 to 12 months
4 suspicious - X-ray or ultrasound-guided core-needle biopsy recommended
4A low suspicion of malignancy
4B moderate suspicion of malignancy
5 high probability of malignancy - core-needle biopsy recommended
6 known cancer proven by biopsy

ULTRASOUND

US1 ULTRASOUND RESULTS (BIRADS)
1 normal
2 clearly benign
3 probably benign - follow-up at 6 to 12 months
4 suspicious - X-ray or ultrasound-guided core-needle biopsy recommended
4A low suspicion of malignancy
4B moderately low suspicion of malignancy
4C high suspicion of malignancy
5 highly suggestive of malignancy - core-needle biopsy recommended
6 known cancer proven by biopsy

US2 TUMOUR SIZE (mm)
_____

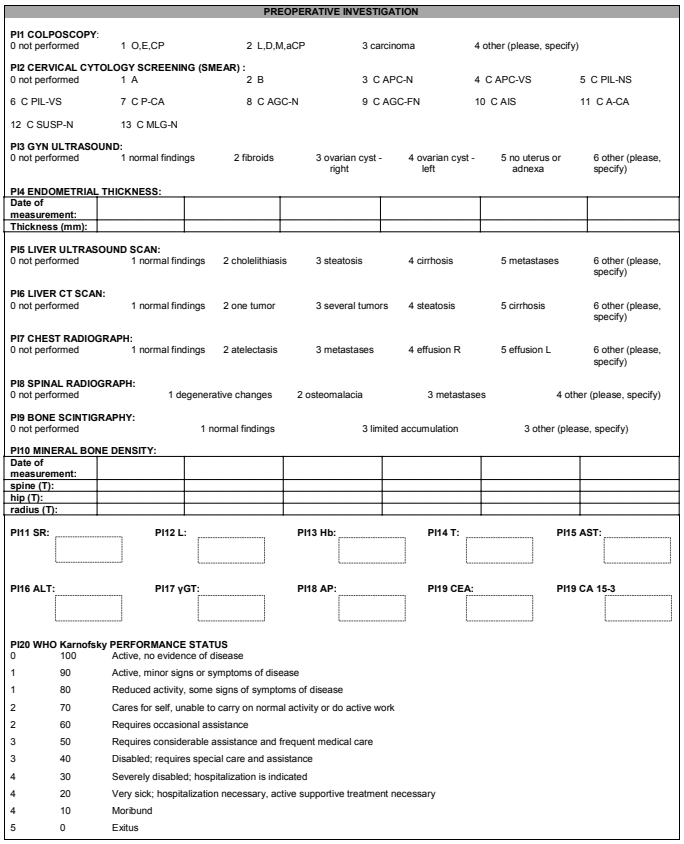
US3 TUMOUR BLOOD SUPPLY
1 decreased
2 increased

US4 AXILLARY LYMPH NODES
0 not suspicious (go to US5 and US6)
1 suspicious

US5 SIZE OF LARGEST LYMPH NODE (mm)
_____

US6 NO. OF SUSPICIOUS LIMPH NODES
_____

FIGURE 3. Clinical examination and breast imaging.



PREOPERATIVE INVESTIGATION

PI1 COLPOSCOPY:
0 not performed 1 O,E,CP 2 L,D,M,aCP 3 carcinoma 4 other (please, specify)

PI2 CERVICAL CYTOLOGY SCREENING (SMEAR) :
0 not performed 1 A 2 B 3 C APC-N 4 C APC-VS 5 C PIL-NS
6 C PIL-VS 7 C P-CA 8 C AGC-N 9 C AGC-FN 10 C AIS 11 C A-CA
12 C SUSP-N 13 C MLG-N

PI3 GYN ULTRASOUND:
0 not performed 1 normal findings 2 fibroids 3 ovarian cyst - right 4 ovarian cyst - left 5 no uterus or adnexa 6 other (please, specify)

PI4 ENDOMETRIAL THICKNESS:

Date of measurement:						
Thickness (mm):						

PI5 LIVER ULTRASOUND SCAN:
0 not performed 1 normal findings 2 cholelithiasis 3 steatosis 4 cirrhosis 5 metastases 6 other (please, specify)

PI6 LIVER CT SCAN:
0 not performed 1 normal findings 2 one tumor 3 several tumors 4 steatosis 5 cirrhosis 6 other (please, specify)

PI7 CHEST RADIOGRAPH:
0 not performed 1 normal findings 2 atelectasis 3 metastases 4 effusion R 5 effusion L 6 other (please, specify)

PI8 SPINAL RADIOGRAPH:
0 not performed 1 degenerative changes 2 osteomalacia 3 metastases 4 other (please, specify)

PI9 BONE SCINTIGRAPHY:
0 not performed 1 normal findings 3 limited accumulation 3 other (please, specify)

PI10 MINERAL BONE DENSITY:

Date of measurement:						
spine (T):						
hip (T):						
radius (T):						

PI11 SR: **PI12 L:** **PI13 Hb:** **PI14 T:** **PI15 AST:**

PI16 ALT: **PI17 γGT:** **PI18 AP:** **PI19 CEA:** **PI19 CA 15-3**

PI20 WHO Karnofsky PERFORMANCE STATUS

0	100	Active, no evidence of disease
1	90	Active, minor signs or symptoms of disease
1	80	Reduced activity, some signs of symptoms of disease
2	70	Cares for self, unable to carry on normal activity or do active work
2	60	Requires occasional assistance
3	50	Requires considerable assistance and frequent medical care
3	40	Disabled; requires special care and assistance
4	30	Severely disabled; hospitalization is indicated
4	20	Very sick; hospitalization necessary, active supportive treatment necessary
4	10	Moribund
5	0	Exitus

FIGURE 4. Investigations before treatment.

ment. Until now, data about 3,600 patients have been included in this computer program.

Twenty-nine anamnestic data focus on known risk factors for breast cancer as well as current symptoms and signs. Among the risk factors, detailed data on family history of breast cancer and other malignancies, reproductive data, use of hormonal therapy, smoking, and use of alcohol were recorded. Detailed data are listed in Figure 2. The anamnestic data ended with signs and symptoms in the breast, such as breast lump, pain, skin changes, nipple discharge, enlarged axillary lymph nodes as well as their duration and general symptoms, such as bone pain, abdominal pain, dyspnoea, cough, neurological symptoms, and loss of weight.

Next section covered a clinical examination with 17 parameters, including inspection and palpation of the breasts and regional lymph nodes, including axillary and supraclavicular lymph nodes. Body mass index data were recorded and data on breast imaging, mammography and ultrasonography of the breast and axillary lymph nodes were collected (Figure 3).

The following section contained data about different extended investigations before treatment: gynaecological examinations (colposcopy, gynaecological ultrasound), imaging examinations of liver, lung and bones and certain laboratory testing with the focus on the most common sites of metastases. At the end of this section, WHO and Karnofsky performance status was recorded (Figure 4).

The section containing data about the surgical procedure and postoperative care included 16 parameters. Date of procedure, type of surgery, use of frozen section, complications during procedure, and placement of drains were recorded immediately after the surgery. Later, the removal of drains, antibiotic therapy and possible complications were added before the patient leaves hospital (Figure 5). For an easy and fast completion of the inquiry, six types of surgical procedures were listed with separate marks for the right and left breast. The most common complications during and after surgery were also listed, including the complications in the breasts, such as bleeding or hematoma, seroma,

SURGERY

S1 DATE OF PRIMARY SURGERY:

S2 DATE OF SECONDARY SURGERY:

S3 INTERVENTION done in primary surgery:
1 tumorectomy ☐R ☐ L
2 quadrantectomy ☐R ☐ L
3 mastectomy ☐R ☐ L
4 SNB ☐R ☐ L
5 axillary clearance ☐R ☐ L
6 tumor bed re-excision ☐R ☐ L
7 other (please, specify) ☐R ☐ L
8 declined by patient

S4 INTERVENTION done in secondary surgery:
1 tumorectomy ☐R ☐ L
2 quadrantectomy ☐R ☐ L
3 mastectomy ☐R ☐ L
4 SNB ☐R ☐ L
5 axillary clearance ☐R ☐ L
6 tumor bed re-excision ☐R ☐ L
7 other (please, specify) ☐R ☐ L

S5 FROZEN SECTION:
0 no (go to O7)
1 yes

S6 FROZEN SECTION RESULTS:
0 benign tumor
1 probably malignant tumor
2 malignant tumor

S7 COMPLICATIONS DURING SURGERY:
0 no
1 bleeding
2 nerve damage
3 vascular damage
4 anesthetic
5 other (please, specify)

S8 BREAST DRAINAGE:
0 no (go to O11)
1 yes

S9 DRAINAGE OUTPUT (mL):

S10 NO. OF DAYS WITH DRAINAGE:

S11 AXILLARY DRAINAGE:
0 no (go to 50)
1 yes

S12 AXILLARY DRAINAGE OUTPUT (ml):

S13 NO. OF DAYS WITH AXILLARY DRAINAGE:

S14 PERIOPERATIVE ANTIBIOTICS:
0 no
1 yes

S15 INTRAOPERATIVE ANTIBIOTICS:
0 no
1 yes

S16 POST-OPERATIVE COMPLICATIONS:
0 no
1 bleeding
2 seroma
3 hematoma
4 wound infection
5 wound dehiscence
6 febrile condition
7 sepsis
8 deep vein thrombosis
9 pulmonary embolism
10 exitus
11 other (please, specify)

S17 DATE OF DISCHARGE FOLLOWING PRIMARY SURGERY:

RADIATION THERAPY

RT1 RADIATION THERAPY :
0 no (go to H1)
1 yes
2 declined by patient

RT2 TYPE OF RADIATION THERAPY:
1 preoperative
2 postoperative
3 radical
4 palliative
5 other (please, specify)

RT3 KIND OF RADIATION THERAPY:
1 beam radiation
2 interstitial brachytherapy
3 other (please, specify)

RT4 DURATION OF RADIATION THERAPY:
From (dd-mm-yyyy): **Until (dd-mm-yyyy):**

RT5 SOURCE OF RADIATION:
1 linear accelerator
2 iodine-125
3 iridium-192

RT6 NUMBER OF FRACTIONS:

RT7 TOTAL RADIATION DOSE (Gy):

RT8 COMPLICATIONS FOLLOWING RADIATION THERAPY:
0 no
1 anemia
2 leukopenia
3 thrombocytopenia
4 dermatitis
5 exitus
6 other (please, specify)

FIGURE 5. Surgery and radiotherapy.

HISTOLOGY

H1 DIAGNOSTIC METHODS:
1 clinical
2 mammogram
3 cytology
4 histology (wide core needle biopsy)
5 histology (biopsy)
6 histology (frozen section)
7 other (please, specify)

H2 FINE-NEEDLE ASPIRATION (FNA):
0 not performed
1 insufficient material
2 repetition due to 1 (1x, 2x, 3x)
3 sufficient material obtained

H3 FINE NEEDLE ASPIRATION (FNA) RESULTS:
1 C1 – sample inadequate for testing
2 C2 – normal breast cells
3 C3 – cells abnormal
4 C4 – highly suspicious of cancer
5 C5 – carcinoma

H4 TUMOUR SIZE (mm):
1. _____
2. _____
3. _____

H5 TUMOR HISTOLOGY (1. | 2. | 3.)
0 not assessed
1 DCIS
2 ductal carcinoma
3 LCIS
4 lobular carcinoma
5 medullary carcinoma
6 mucinous carcinoma
7 tubular carcinoma
8 ductal + lobular carcinoma
9 other (please, specify)

H6 CLEAR MARGINS (1. | 2. | 3.)
0 no
1 yes
distance to margin in mm:

H7 SENTINEL NODE BIOPSY (SNB)
R L
0 no 0 no
1 yes 1 yes

H8 NO. OF REMOVED SN:
R L

H9 CYTOLOGY OF SNB:
0 negative
1 positive

H10 HISTOLOGY OF SNB:
0 negative
1 positive
2 micrometastases

H11 AXILLARY CLEARANCE:
0 none
1 yes

H12 NO. OF AXILLARY LIMPH NODES:
R L

H13 NO. OF POSITIVE LIMPH NODES:
R L

H14 AXILLARY METASTASES' DIAMETER:
R L

H15 ESTROGEN RECEPTORS:

	R	L
0 not tested	0	0
1 not found	1	1
2 present _____%	2	2
3 no data available in %	3	3

H16 PROGESTERONE RECEPTORS:

	R	L
0 not tested	0	0
1 not found	1	1
2 present _____%	2	2
3 no data available in %	3	3

H17 HER-2 (HISTOCHEMICAL/IMMUNOHISTOCHEMICAL):
0 not assessed
1 negative (0)
2 weakly positive (1+)
3 moderately/borderline positive (2+)
4 strongly positive (3+)

H18 HER-2 (FISH):
0 negative
1 positive

H19 uPA:
0 not assessed
1 assessed _____ ng/mg prot.

H20 PAI-1:
0 not assessed
1 assessed _____ ng/mg prot.

H21 Ki-67:
0 not assessed
1 assessed _____

FIGURE 6. Histopathology.

wound infection, wound dehiscence and systemic complications, such as fever, deep vein thrombosis and pulmonary embolism.

For radiation therapy, eight boxes were designed: type, dates of starting and ending radiotherapy and possible complications (Figure 5). As in the case of surgery, the most common type and complications of radiotherapy were provided in the inquiry. Because radiotherapy was performed at the Department of Oncology, data about this part of treatment were filled after complete treatment, at the first follow-up visit at the latest.

In the next section, data on cytological and histopathological examination of tumour and lymph nodes were collected. The first part of this section included data on preoperative diagnostics, which could be collected prior to the primary treatment. The inquiry included data on the tumour histology before and after surgery, cytology and histology of sentinel node biopsy (SNB) and/or axillary node dissection and the main predictive and prognostic biomarkers, oestrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2) and proliferation marker Ki67 (Ki67) (Figure 6). Full data on histopathology were usually available after the patient leaves the hospital; hence, this part of the inquiry was completed later on.

Since the systemic therapy represented an important part of breast cancer treatment in the control and cure of breast cancer, a relatively large part of the inquiry was dedicated to this issue.

Detailed information about adjuvant or neoadjuvant chemotherapy was collected in the special section of the inquiry boxes during treatment (Figure 7). Among others, this data included the date of each chemotherapy cycle and chemotherapy regimen. The presence of the adverse events during chemotherapy was collected in the Chemotherapy section. Detailed data regarding the type and severity of adverse events were collected in the section Adverse events.

A separate sheet contained data on systemic anti-cancer treatment, including chemotherapy,

hormonal and targeted therapy, applied as neoadjuvant or adjuvant treatment. The same page contained boxes for systemic treatment in case of recurrent disease. The most frequently used agents were already listed and categorized for chemotherapy, hormonal therapy, and targeted therapy. Over the past decades, adjunctive and supportive therapy of breast cancer have evolved substantially. In the inquiry, the data on bisphosphonates, erythropoietin and granulocyte colony-stimulating factor (G-CSF) were collected during the systemic treatment (Figure 8).

The last section of the inquiry was follow-up sheet (Figure 9). All nine boxes were completed at every follow-up visit. Data collected at follow-up were limited to performance status, pain, clinical examination, mammography, laboratory tests, and the clinical state of the patient.

All data collected with the paper inquiry were recorded using the computer program *Onko-Online* for processing data and statistical analysis. The program enables to find, list and sort data in a quick and easy manner. The existing data could be modified or new data could be added, if necessary.

ST1 CHEMOTHERAPY CYCLE / TREATMENT LEVEL:	1	2	3	4	5	6
ST2 DATE:						
ST3 BODY WEIGHT (kg):						
ST4 HEIGHT (cm):						
ST5 SURFACE (m^2):						
ST6 PERFORMANCE STATUS: (See P21) 0 3 1 4 2 5						
ST7 EXAMINATION: 0 NAD 3 lymphedema 1 tumor 4 metastasis 2 hydrothorax 5 other (specify)						
ST8 CHEST RADIOGRAPH: 0 NAD 2 hydrothorax 1 metastases3 other (specify)						
ST9 LIVER ULTRASOUND SCAN: 0 NAD 2ascites 1metastases3 other (specify)						
ST10 BONE SCINTIGRAPHY: 0 NAD (nothing abnormal detected) 1 metastases (site) 2 diffuse accumulation (site)						
ST11 BONE RADIOGRAPHY: 0 NAD (nothing abnormal detected) 1 metastases (site) 2 diffuse changes (please, specify)						
ST12 Ca 15-3						
ST13 DOSE REDUCTION (%)						
ST14 REASON FOR REDUCTION a ↓L c liver dysfunction b ↓T d renal dysfunction						
ST15 CYTOTOXIC 1: (mg)						
ST16 CYTOTOXIC 2: (mg)						
ST17 CYTOTOXIC 3: (mg)						
ST18 G-CSF (dose)						
ST19 ANTIEMETIC (mg)						
ST20 PATHOLOGY LAB. RESULTS biochemistry (AP, GT…) marker (CEA) other (please, specify)						
ST21 VOMITING: 0 no 2 6x–10x 1 1x–5x 3 > 10x						
ST22 ADVERSE EVENT: (See page 6) 0 no 1 yes						

FIGURE 7. Adjuvant or neoadjuvant chemotherapy.

Discussion

The breast cancer inquiry collected extended information on altogether 167 questions about breast cancer patient medical history, clinical status, treatment, and its outcome.

Among the risk factors, we recorded data known to be associated with high risk for breast cancer. It is well known that there is a two-fold increase in the risk of developing breast cancer for women with breast cancer in their first-degree family, especially among women with a first-degree relative diagnosed before the age of 50.[6,7] Among the reproductive data, young age at menarche, late menopause, late age at first pregnancy, low number of deliveries, spontaneous or induced abortions, and lack of breastfeeding are known to increase the risk of breast cancer.[8,9] Known risk factors also include hormonal contraception and hormonal replacement therapy, although the absolute increase in risk, especially for contraception, is small.[10,11] Some studies reported a link between infertility and increased breast cancer risk, while others were not able to find a connection.[12, 13] The results of recently published data in literature strongly support the role of cigarette smoking in breast cancer etiology.[14] The risk of breast cancer is significantly increased by alcohol consumption as well.[15] Data on body mass index were included, since it is known that obesity is associated with an increased relative risk, especially for postmenopausal receptor-positive breast cancer.[16] Known risk factors for breast cancer were included to determine the frequency of these risk factors in our population. Moreover, the knowledge of these risk factors in a subset of patients could lead to a better understanding of different factors involved in the breast cancer development.

Typical local signs and symptoms for breast cancer are: a breast lump, usually painless; skin retraction, nipple retraction, nipple discharge, and swelling in the armpit.[17] All these signs were listed in the inquiry as well as palpable lymph nodes in the axilla.

We also added some typical signs of a metastatic disease (bone pain, dyspnoea, persistent cough, abdominal pain, weigh loss), although primary metastatic cancer is relatively rare. According to our registry, in Slovenia 7.1% of patients were presented with primary metastatic disease in 2015.[1] The data in the literature for developed countries

TREATMENT SCHEME (TS1) LEVEL OF TREATMENT	(ST2 – ST7) CHEMOTHERAPY				(ST8 – ST12) HORMONAL THERAPY				(ST13 – ST19)	TARGETED (BIOLOGICAL) TREATMENT			(ST20 – ST22) ADJUVANT THERAPY		ST23 OUTCOMES, RESPONSE
	0 no 1 yes	1 cyclophosphamide 2 methotrexate 3 5-fluorouracil 4 capecitabine 5 doxorubicin 6 epirubicin 7 paclitaxel 8 docetaxel 9 cisplatin 10 carboplatin 11 vinorelbine 12 other (specify)	No. of cycles Frequency of cycles	Date - since Date - since	0 no 1 yes	1 tamoxifen (Nolvadex) 2 anastrazole (Arimidex) 3 exemestane (Aromasin) 4 letrozole (Femara) 5 fulvestrant (Faslodex) 6 GnRH (Zoladex) 7 other (specify)	Dose	Date - since Date - until	0 no 1 trastuzumab 2 lapatinib 3 bevacizumab 4 other (specify)	Dose cumulative dose	No. of cycles Frequency of cycles	Date - since Date - until	1 Bisphosphonates 2 Erythropoietins 3 GCSF 4 other (specify)	Date - since Date - until	
NON-ADJUVANT															0 disease-free 1 progress during chemotherapy and/or targeted (biological) treatment 2 progress following chemotherapy and/or targeted (biological) treatment 3 condition unknown
ADJUVANT															0 disease-free 1 progress during chemotherapy and/or targeted (biological) treatment 2 progress following chemotherapy and/or targeted (biological) treatment 3 condition unknown
PRIMARY METASTATIC DISEASE															
1. RELAPSE (LINE) 0 no 1 yes, clinical 2 yes, biochemical 3 yes, x-ray, ultrasound, scintigraphy 4 yes, confirmed by biopsy															0 complete remission (CR) 1 partial remission (PR) 2 stable disease (SD) 3 progressive disease (PD) 4 condition unknown
DATE 1. RELAPSE															
2. RELAPSE (LINE) 0 no 1 yes, clinical 2 yes, biochemical 3 yes, x-ray, ultrasound, scintigraphy 4 yes, confirmed by biopsy															0 complete remission (CR) 1 partial remission (PR) 2 stable disease (SD) 3 progressive disease (PD) 4 condition unknown
DATE 2. RELAPSE															
3. RELAPSE (LINE) 0 no 1 yes, clinical 2 yes, biochemical 3 yes, x-ray, ultrasound, scintigraphy 4 yes, confirmed by biopsy															0 complete remission (CR) 1 partial remission (PR) 2 stable disease (SD) 3 progressive disease (PD) 4 condition unknown
DATE 3. RELAPSE															
4. RELAPSE (LINE) 0 no 1 yes, clinical 2 yes, biochemical 3 yes, x-ray, ultrasound, scintigraphy 4 yes, confirmed by biopsy															0 complete remission (CR) 1 partial remission (PR) 2 stable disease (SD) 3 progressive disease (PD) 4 condition unknown
DATE 4. RELAPSE															

CR = complete response (disappearance of all target lesions); PD = progressive disease (20% increase of sum of the longest target lesions dimension); PR = partial response (30% decrease of sum of all target lesions dimension); SD = stable disease (minor lesions not qualifying for CR/PR/PD)

FIGURE 8. Treatment scheme.

are similar, approximately 5-10% of all breast cancer patients were presented with distant metastases at initial diagnosis.[18]

Clinical breast examination is not a reliable diagnostic tool[19], but it has to be performed in all known breast cancer patients when planning primary treatment - surgical or neoadjuvant systemic therapy. Ultrasound preoperative examination of axilla was routinely performed to avoid two-stage axillary surgery in selected patients.[20, 21] At the moment, MRI was not included in the inquiry. Since both MRI and digital breast tomosynthesis are nowadays common diagnostic procedures in breast diagnostics, we intended to add both procedures to the pre-treatment diagnostics.

According to Slovenian recommendations for stage I and II breast cancer, laboratory tests, including blood count, liver function tests, alkaline phosphatase, calcium levels, and chest X-ray were routinely performed.[22] In case of clinical symptoms and/or pathological laboratory results as well as in all stage III and IV patients, thoracic and abdominal CT scan and bone scintigraphy were performed.[22]

In the inquiry section covering a surgical procedure, breast reconstruction was not included, since this type of procedure was performed at the Department of Plastic and Reconstructive Surgery at the University Medical Centre Maribor and not within our department. Breast reconstruction is an important part of breast cancer management which has evolved significantly in the past decades because of advances in reconstructive strategy.[23] It is oncologically safe and associated with high satisfaction rates.[24] In the case of breast reconstruction, data was recorded in the inquiry during the first follow-up visit.

Over the last two years, radiation therapy for breast cancer patients has mostly been administered at our hospital at the Department of Oncology at the University Medical Centre Maribor, but some patients still receive therapy at the Institute of Oncology in Ljubljana. All data concerning radiotherapy, including complications, were collected at the first follow-up visit.

According to the data in literature, fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB) have similar values of diagnostic accura-

S1 DATE:	S2 TYPE OF EXAMINATION: 1 outpatient clinic 2 hospital	S3 WHO PERFORMANCE STATUS: 0 asymptomatic, but completely ambulatory 1 symptomatic, 2 symptomatic, up and about more than 50% of waking hours 3 symptomatic, confined to bed or chair more than 50% of waking hours 4 confined to bed	S4 PAIN: 0 no pain 1 mild pain 2 moderate pain 3 severe pain	S5 EXAMINATION 1 NAD (nothing abnormal detected) 2 tumor (size) 3 lymph nodes in axilla 4 lymph nodes above collar bone 5 hand edema 6 other (describe)	S6 MAMOGRAPHY: 0 N/A D 1 NAD (nothing abnormal detected) 1 2 suspicious findings 2 3 carcinoma 3 4 other (specify) 9	S7 LABORATORY: 1 NAD (nothing abnormal detected) 2 high ESR levels 3 anemia 4 leukopenia 5 leukocytosis 6 high AST levels 7 high ALT levels 8 high γGT levels 9 high ALP levels 10 high CEA levels 11 high CA 15-3 12 other (specify)	S8 CONDITION ASSESSMENT: 0 alive, no symptoms (CR or DF) 1 alive, partial remission (PR) 2 alive, stable disease (SD) 3 alive, relapse 4 alive, progressive disease (PD) 5 alive, condition unknown 6 ex due to breast malignancy 7 ex during treatment 8 ex due to other disease, no breast symptoms 9 ex due to other disease, breast symptoms present 10 ex, cause unknown 11 condition unknown	S9 NOTES:

FIGURE 9. Follow-up.

cy.[25, 26] We routinely used CNB as the first method in breast cancer diagnostics, because hormonal receptor (HR) status and expression of HER2 can be tested. Sometimes, this information was crucial for planning the treatment, e.g. neoadjuvant systemic therapy.

TNM classification of breast cancer was not included in the computer program and it served as a tool to define the correct stage in the general data (Figure 1 – G14).

The data set about the systemic treatment has been designed to provide access to quick and transparent information on systemic therapy for patients and enable easier decision-making processes for further treatment in case of disease progression. Every list of chemotherapy, hormonal and targeted therapy was given the option "others" to name drugs, which were not included. Novel therapeutic approaches included immunologic therapies, PARP inhibitors, PI3K inhibitors, and CDK4/6 inhibitors, and others to be added to the inquiry at any time.

In the inquiry, information on date of diagnosis and date of starting (different) treatment were included. The inquiry collected the date of first and second surgery, date of all neoadjuvant or adjuvant chemotherapy cycles, beginning and ending date of radiotherapy, and beginning and ending date for all types of systemic treatments. There are data in the literature suggesting that time to start of adjuvant treatment might have an influence on survival.[27] Delays to adjuvant radiotherapy are also related with decreases in survival of patients with locally advanced tumours.[28]

The purpose of a follow-up was surveillance for recurrence, management of long-term effects of cancer treatment, and management of medication side effects. At our department, follow-up was performed over a time period of 10 years. According to Slovenian recommendations[22], follow-up visits for asymptomatic patients were performed every six months for the first 3 years and then annually. At each visit, clinical examination was performed. Patients underwent mammography on

a yearly basis. Laboratory tests were indicated in case of clinical symptoms. Liver ultrasound, chest radiography, bone scan, and other investigations were performed only in case of clinical symptoms or pathological laboratory tests. At the end of the follow-up visit, treatment response rate was estimated. Treatment response rates were mostly evaluated on the basis of WHO criteria[29], although new and updated criteria had been published for more precise and objective response.[30,31]

There is no evidence that the detection of asymptomatic distant metastases leads to a longer survival.[32] Some data indicated that the detection of isolated loco-regional or contra-lateral breast cancer recurrences in patients without symptoms has beneficial impact on survival of breast cancer patients when compared to late symptomatic detection[33]; however, it was shown that only 40% of the isolated loco-regional recurrences in asymptomatic patients were detected during routine examination.[34] But, the vast majority of the patients took advantage of the follow-up and one of the important goals of the follow-up care is to offer psychological support and reassurance by their physician.[35, 36]

The type of treatment in patients who were metastatic at first presentation was recorded in the same way as for patients with localised or regional cancer. In case of disease relapse after primary treatment, data about the date of relapse, site of relapse and treatment of relapse were recorded in the section General data. Detailed data about systemic treatment of relapse were recorded also in the Treatment scheme section.

Conclusions

The clinical cancer registry plays an important role in the evaluation of clinical practice with the purpose to improve organisation in daily clinical work and treatment of the disease. It allows us to continuously compare treatment results with national and international standards. The data can also be used for research projects and studies on cancer survivorship.

The computer program *Onko-Online* allows quick and reliable processing and analysis of 167 different data obtained from breast cancer patients, i.e. general information, medical history, diagnostics, treatment and follow-up. The computer program allows us to follow the timing of different treatments procedures to assure optimal treatment for all breast cancer patients.

A potential limitation of the registry is the incomplete or incorrect data input. With this amount of data collected by different healthcare providers there is a risk that a mistake will occur, but not in the extent to which it could influence the reliability of the data.

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