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 diseases¹. 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-
Clinical examination and breast imaging.

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,
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 neo-adjuvant 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.

**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. 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. Known risk factors also include hormonal contraception and hormonal replacement therapy, although the absolute increase in risk, especially for contraception, is small. Some studies reported a link between infertility and increased breast cancer risk, while others were not able to find a connection. The results of recently published data in literature strongly support the role of cigarette smoking in breast cancer etiology. The risk of breast cancer is significantly increased by alcohol consumption as well. 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. 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. 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, weight 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. The data in the literature for developed countries...
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 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 accur-
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, although new and updated criteria had been published for more precise and objective response.

There is no evidence that the detection of asymptomatic distant metastases leads to a longer survival. 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; however, it was shown that only 40% of the isolated loco-regional recurrences in asymptomatic patients were detected during routine examination. 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.

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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