Which tools can I use in daily clinical practice to improve tailoring of treatment for breast cancer?
The 2007 St Gallen guidelines and/or Adjuvant! Online

T. Čufer
Institute of Oncology, 1000 Ljubljana, Zaloska 2, Slovenia

Introduction
The prognosis of early breast cancer (EBC) has improved substantially during the last few decades. Despite the persisting rise in the breast cancer incidence, the mortality rates have been declining since the early 1990s. A reduction of 17% and 24%, respectively, was recorded in Europe and in the United States from 1990 to 2002 [1, 2]. These trends have been equally attributed to the effect of early detection, i.e. organized screening programs and to the introduction of adjuvant systemic therapies in routine clinical practice in the 1980s [2]. With the incorporation of more effective and less toxic hormonal and cytotoxic agents and to an even greater extent with the introduction of new targeted therapies and tailored treatment strategies in adjuvant therapy, further improvements in control of EBC are to be expected. However, the major question at the present moment is how to best tailor the adjuvant treatment in each individual patient in a routine clinical practice? With a growing bulk of new information and evidence-based data it is very difficult for each individual doctor to deal with all the information and to make an informed decision on the best possible adjuvant therapy for each particular patient. There are various tools available nowadays that can help to estimate the prognosis and to predict the possible effect of each of the treatment modalities, i.e. hormonal therapy, chemotherapy and targeted therapy, in each EBC patient. The two tools most commonly used in Europe are Adjuvant! Online and the St Gallen guidelines.

Adjuvant! Online
Adjuvant! is one of the most complex and ambitious tools that can be used to estimate objectively the risk of breast cancer relapse and death, and the likely benefit of adjuvant systemic therapy for women with EBC after radical local therapy [3]. Adjuvant! Online [4] is a simple-to-use computer program to produce prognostic estimates of outcome with and without therapy, based on the estimates of individual patient prognosis and the efficacy of different adjuvant therapy options. It is easily accessible on the web and free of charge. Of note, the model cannot be used to provide estimates for patients with residual disease after surgery, patients receiving neo-adjuvant systemic therapy and patients with rare histological tumor types (pure tubular, papillary or mucinous cancer).

Because of the complexity of the information and the terminology used, this program is not designed to be used by patients directly, but is designed as a tool to be used by health professionals familiar with the issues in the adjuvant treatment of breast cancer. They are supposed to share and discuss the information with their patients.

Estimates of prognosis are based mainly on the Surveillance, Epidemiology and End-Results (SEER) registry estimates of the outcome of breast cancer patients in the general population of women aged 36–69 diagnosed with breast cancer in the United States. Estimates of the efficacy of adjuvant hormonal therapy and chemotherapy are based mainly on the proportional risk reduction (PRR) obtained from the Early Breast Cancer Trialists’ Collaborative Group meta-analyses (Overview) [5–7] and from individual trials of adjuvant systemic therapy. Since the Overview suggests that the benefit of adjuvant chemotherapy or hormonal therapy occurs independently of whether the other modality is used, in Adjuvant! Online the efficacy of combined chemo-endocrine therapy for each individual case is derived as the product of the individual PRR from hormonal therapy and polychemotherapy.

In the current Adjuvant! Online version 8.0 the prognostic estimates are based on age, menopausal status, co-morbidity, estrogen receptor (ER) status, tumor grade, tumor size and the number of involved axillary nodes. Menopausal status is determined automatically and based on the Overview assumption that the age of 50 represents the cut-off point between pre- and postmenopausal status. Each adjuvant therapy effectiveness estimate is based on the Overview and individual trials data adjusted for age (i.e. menopausal status) and for ER status in only postmenopausal patients. Adjuvant! Online version 8.0 provides us with information on the potential efficacy of tamoxifen and third-generation aromatase inhibitors (AIs) in postmenopausal ER-positive patients; of tamoxifen, ovarian suppression or both in premenopausal ER-positive patients and of a wide range of chemotherapeutic schedules, from CMF-like first generation schedules to the complex anthracycline-based second generation (CAF, CEF; FEC100, AC-T) and anthracycline-taxane-based third-generation (FEC-Doce, TAC, dose-dense AC-T) schedules.
After entering the data for each individual patient the risk of relapse and the risk of dying due to cancer or to any other reasons as well as proportional benefits gained from hormonal therapy, chemotherapy or both for being alive and/or without relapse at 10 years are calculated and displayed. Calculations of outcome earlier than 10 years can be done, but any projections of outcome beyond 10 years are speculative.

Due to a limited follow-up period for some types of therapy such as taxane-based chemotherapy and hormonal therapy by AIs shorter period PRR can only be calculated and presented. The new Adjuvant! Online 9.0 version, which will take into consideration the prognostic impact of HER2 status and will also offer information on the additional proportional benefits due to trastuzumab therapy, is about to be released.

The validity of the Adjuvant! Online model and its applicability to EBC patients was confirmed using the British Columbia Cancer Agency (BCCA) breast cancer unit database [8]. Across more than 4000 patients 10-year predicted and observed outcomes were within 1% and Adjuvant! Online was found to be a very reliable tool to provide estimates of 10-year risk for overall survival (OS), breast cancer-specific survival (BCSS) and event-free survival (EFS) without adjuvant systemic therapy. The predictions of absolute benefits of adjuvant systemic therapy were generally reliable but were overly optimistic for the subgroups with adverse prognostic factors not accounted for by the model and for younger patients. This could be partially compensated by using the prognostic factor impact calculator (PFIC) inherent to Adjuvant! Online. It allows for risk assessment adjustment for the established prognostic factor, if the prevalence of the positive test and the relative risk conferred is known.

Adjuvant! Online was confirmed as a reliable tool in estimating the risk of relapse/death and the average benefit from adjuvant systemic therapy; however, the users need to be aware of its limitations and drawbacks.

The major drawback comes from its simplified and averaged model. The prognostic prediction is based mainly on the anatomical stage of disease (tumor size, node involvement); out of biological markers only tumor grade and ER positivity are included in the model. Nowadays, a set of data coming from the extensive work carried out in the field of molecular biology teaches us that the prognosis of EBC can differ substantially in the subsets of patients defined by molecular profiling assays [9–11]. There is a special Adjuvant! Online version available that gives us the estimates of risks and proportional benefits of hormonal and chemotherapy in ER-positive node-negative disease according to the molecular prognostic score determined by OncotypeDX. However, this version allows for more precise treatment tailoring only in the limited number of ER-positive node-negative patients that have access to OncotypeDX. There is growing evidence that also among patients with larger tumors and/or node-positive disease subsets of patients with an excellent prognosis without any systemic therapy or with tamoxifen alone can be identified by molecular profiling assays [12, 13]. In addition, these patients seem to have a much smaller proportional benefit from any adjuvant chemotherapy [13, 14]. The user has to be aware of these new data which have not yet been included in the model.

Another limitation inherited in the current Adjuvant! Online version relates to the estimation of treatment effectiveness of both hormonal therapy and chemotherapy adjusted only for age and ER positivity in postmenopausal patients. No fine tuning according to the level of ER positivity, progesterone receptor (PR) status, tumor grade, proliferation markers and HER2, already known predictors for response to both hormonal therapy and chemotherapy, is yet possible [15]. Although there is growing evidence that the proportional benefits from any chemotherapy and especially from second- and third-generation schedules and dose-dense chemotherapy are much less extensive in ER-positive disease [16–18], this knowledge is not implemented in the current version of Adjuvant! Online. There is also a number of simplifying approximations with reference to time-dependent terms for the risk of breast cancer-related events that might be only delayed rather than prevented, inherent in the model. For some treatment modalities like third-generation AIs, dose-dense chemotherapy and some anthracycline–taxane schedules, estimations of treatment efficacy are limited to a period <10 years due to the limited follow-up period of the trials. Last but not least, one has to be aware that the validity of the assumptions inherent in Adjuvant! Online and its applicability to women beyond the population used to develop the model is uncertain. The extent to which the benefits of the adjuvant systemic therapy observed in the frame of the Overview and other individual trials translate to the population of patients treated in a routine clinical practice, outside the controlled conditions of clinical trials, is unknown. Most of the information on treatment efficacy comes from the meta-analysis of clinical trials in which only fit patients without major co-morbidities and <70 years of age were included. There is a question whether a rough adjustment for co-morbidity allows for an accurate estimate of treatment efficacy in elderly and fragile patients. In addition, the validation study performed by BCOU pointed out the need to incorporate young age as an independent adverse prognostic factor [8].

In summary, Adjuvant! Online is a useful tool to aid physicians and patients in making joint decisions on the best possible adjuvant systemic therapy for each individual patient if used by a skilled oncologist with a profound knowledge of adjuvant systemic therapy. Adjuvant! Online can support decisions, but should never substitute for good clinical judgment.

**St Gallen guidelines**

There is a variety of guidelines available to set the therapeutic paths in EBC and to provide information on the best possible treatment in specific patient groups. The main purpose of guidelines is to digest the ever-growing amount of new evidence-based data provided by clinical trials and to integrate them into clinical practice. They are developed to enhance the quality of care by reducing under-treatment, over-treatment and wrong treatment.

In the field of EBC the most appreciated guidelines are those of the National Institutes of Health (NIH) and the National Comprehensive Cancer Network (NCCN) [19], developed in...
the USA; and the European Society for Medical Oncology (ESMO) Clinical Recommendations [20] and St Gallen guidelines developed in Europe. NIH and NCCN guidelines are very precise and comprehensive, ESMO Clinical Recommendations are minimal and as such most useful for countries with limited resources while the advantage of the St Gallen guidelines is that they are quite simple but still tailored to the needs of specific patients subgroups. St Gallen guidelines and recommendations are designed by a panel of experts that meets every 2 years at St Gallen, Switzerland to reach a consensus on the implications of the current evidence-based data for patient treatment selection. The last consensus was published in Annals of Oncology in 2007 [21]. Even though the St Gallen guidelines tend to be simple, together with the comprehensive panel recommendations they provide very solid and updated evidence-based knowledge and a good perspective on how to use evidence-based data intelligently in our routine clinical practice. The validity of the St Gallen guidelines was evaluated among Canadian women diagnosed with EBC between 1988 and 1994 and treatment according to the consensus recommendations was associated with improved survival in this population [22].

The historical shift in thinking of risk and responsiveness to systemic therapy was achieved at the St Gallen 2005 conference. Rather than the previous approach which built treatment allocation mainly on risk assessment, a fundamental change in treatment allocation based primarily on target selection was introduced [23]. At that time the only targeted therapy with an identifiable target and proven efficacy was hormonal therapy. Therefore the Panel affirmed that the first consideration is endocrine responsiveness, and prognosis per se was considered less relevant for treatment selection for the first time. In addition, axillary lymph node involvement no longer automatically defined high risk and an intermediate risk category was introduced. In line with this orientation and new data on the additional contribution of targeted therapy in HER2-positive disease the most recent St Gallen 2007 guidelines and recommendations incorporated HER2 status in addition to hormone receptor (HR) status as the primary determinants of treatment allocation [21]. Six categories according to HR status and HER2 status were recognized; three according to HR status: highly endocrine responsive, incompletely endocrine responsive and endocrine non-responsive, and two according to HER2 status: HE2 positive and HER2 negative. The panel accepted endocrine responsiveness, either high or incomplete, to assign hormonal therapy and HER2 positivity to assign trastuzumab.

Chemotherapy was assigned as the only option for the endocrine non-responsive, HER2-negative category and to all HER2-positive categories as conventional therapy followed by trastuzumab.

Chemotherapy is being considered in the hormone-responsive, HER2-negative category when the sufficiency of hormonal therapy alone is uncertain either due to incomplete hormone responsiveness or due to a high risk defined by grade, tumor size or node involvement. The determinants of risk remain tumor size, nodal involvement, tumor grade and age. It is of note that HR expression and overexpression or amplification of HER2 are again included among risk factors. Even though the choice of treatment modalities as well as the treatment allocation guidelines by therapeutic target and risk categories remain quite simplified and averaged at first look (Table 1), the comprehensive list of Panel recommendations offers a good insight into the dissection of the Overview data and provides data of retrospective subset analyses of individual clinical trials that is of paramount importance for the understanding of breast cancer heterogeneity and for optimal treatment selection in each individual patient. In addition, the Panel defines the possible side-effects of each individual treatment modality that may diminish the effect of a particular therapy in the whole patient population and even more in specific subsets of patients such as patients with co-morbidities or frail, elderly patients.

The main dilemma in adjuvant systemic therapy of breast cancer nowadays is which patients benefit from chemotherapy, and the major drawback of the current St Gallen guidelines is within this topic. Chemotherapy is recommended for the HR-negative/HER2-negative category and for all HER2-positive categories, which seems reasonable; for triple negative disease, with its inherited bad prognosis, chemotherapy still represents the only available therapeutic option and the efficacy of adjuvant trastuzumab was confirmed only if added to chemotherapy in five large trials [24]. However, in the current guidelines chemotherapy followed by hormonal therapy remains the preferable treatment option also for patients with endocrine-responsive, HER2-negative disease and intermediate or high risk of relapse, determined by nodal involvement, which remains controversial. Already at the time when the guidelines were adopted the preliminary data derived from the retrospective observations performed in the frame of large CALGB, SWOG [17, 25] trials and in the neo-adjuvant setting [18] clearly showed that the added benefit from chemotherapy in the category of hormone-responsive disease seems to be very small even in anatomically more widespread disease.

Emerging data show that by using 21-gene recurrence score or 70-gene expression assays in the group of patients with node-positive disease, a subgroup with a good prognosis without any systemic therapy or hormonal therapy can be

Table 1. Choice of treatment modalities St Gallen 2007

<table>
<thead>
<tr>
<th>HER2-negative</th>
<th>HER2-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly endocrine responsive</td>
<td>Incompletely endocrine responsive</td>
</tr>
</tbody>
</table>
| HT (± CT)
CT | HT (± CT)
CT | CT |
| Trastuzumab + CT + HT | Trastuzumab + CT + HT | Trastuzumab + CT |

*aConsider adding chemotherapy according to risk.
CT, polychemotherapy; HT, hormonal therapy.
identified [12, 13]. Therefore the guideline for chemotherapy in the endocrine-responsive, HER2-negative category of patients with high risk according to lymph node involvement becomes even more controversial. The Panel was aware of the threat of overtreatment in this category and pointed out a difficult decision in this subgroup of patients that needs to take into consideration, in addition to tumor size and nodal involvement, also biological characteristics available, such as grade, peri-tumoral vascular invasion and other proliferative markers.

Another dilemma comes from the rapid evolving field of molecular oncology with new developments in the fields of targeted therapy emerging every day and thus raising a big question mark over the <2-year-old guidelines. Already in 2006 when a large amount of new data on trastuzumab efficacy emerged within a couple months, panelists emphasized how new information influences guidelines and how cautious one has to be when using guidelines for adjuvant therapy selection in a rapidly changing environment.

**conclusion**

In the era of molecular oncology guidelines can only provide us with the basic diagnostic and treatment algorithms in the frame of which one needs to combine individual patient data with the updated knowledge of molecular and medical oncology in order to find the best possible adjuvant therapy for each individual patient. As we shift from an era of empirical oncology to the era of molecular oncology with individualized/personalized treatment approaches, we must be aware of the fact that guidelines can and should only be used by experienced oncologists with a profound knowledge of new developments in both molecular and medical oncology. As long as we respect this fact and restrain from blindly following the guidelines in our routine clinical practice, they will remain a valuable tool for better breast cancer control.

**disclosures**

No significant relationships.

**references**


