Long-term side effects of adjuvant breast cancer treatment

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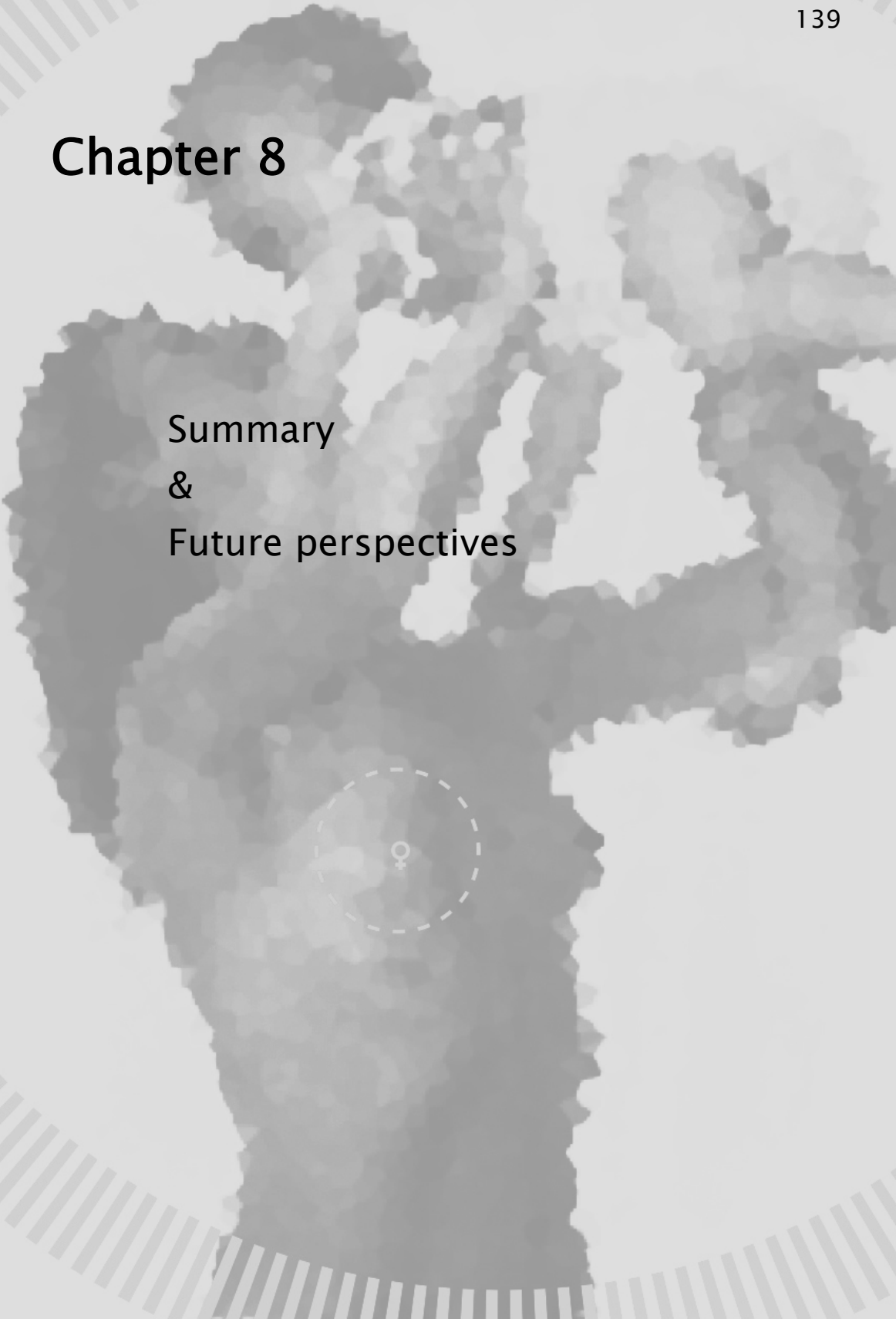
Chapter 8

Summary & Future perspectives



SUMMARY

Breast cancer is the most common malignancy in women. Breast cancer accounts for one-third of all cancers in females and 24% of the patients are younger than 55 years of age. More than 10% all Dutch women will develop breast cancer and 70-80% of all breast cancer patients will survive over 5 years.

In the absence of distant metastases, patients receive loco-regional therapy with or without adjuvant systemic therapy. Loco-regional therapy consists of either a modified radical mastectomy, in some cases followed by local radiotherapy or breast-conserving surgery with removal of the primary tumor and axillary lymphadenectomy followed by irradiation. Adjuvant therapy consisting of chemotherapy, hormonal treatment and the antibody trastuzumab against the epidermal growth factor *HER2*, or a combination have successfully resulted in a lowering of the risk of recurrence and death of this disease. The side effects of adjuvant treatments however can cause physical and psychological problems and the number of patients receiving adjuvant systemic therapy is rising. The higher change to survive in combination with the rising number of treated patients makes the long-term side effects of breast cancer treatment of utmost value. Health Related Quality of Life (HRQoL) is a broad concept, which takes many factors into account, including physical, emotional, sexual, social, and cognitive functions, as well as symptoms of disease and treatment. All these various functions and symptoms are assessed by and from the perspective of the patient. Better knowledge about the impact of adjuvant therapy on HRQoL is important for the evaluation of treatment, for adequate information to patients about future health effects, for treatment decision by physicians and patients and for interventions that reduce the negative effects of the treatment.

This thesis focuses on a number of potential long-term side effects of adjuvant breast cancer treatment.

Because of the dismal prognosis of patients with extensive axillary nodal involvement, over the last 10 years a variety of new treatment regimens has been tested. These include adjuvant dose-dense, as well as high-dose chemotherapy with hematopoietic stem-cell reinfusion. In a large multicenter prospective Dutch study, patients were randomized between a conventional and high-dose chemotherapy regimen, both followed by radiotherapy and tamoxifen. In this study HRQoL was included as a secondary endpoint.

In **Chapter 2** we evaluated and compared HRQoL after conventional- and high-dose adjuvant chemotherapy in patients with high-risk breast cancer.

Patients were randomized between these regimens and both were followed by radiotherapy and tamoxifen. HRQoL was evaluated until disease progression, using the Short-Form (SF-36), Visual Analogue Scale (VAS) and Rotterdam Symptom Checklist (RSCL) and assessed every 6 months for 5 years following randomization. For the SF-36 data from healthy Dutch women with the same age distribution served as reference value.

A total of 804 patients (405 conventional-dose, 399 high-dose chemotherapy) were included. Median follow-up was 57 months. Directly after high-dose chemotherapy HRQoL decreased more compared to conventional chemotherapy for all SF-36 subscales. After 1 year the reference value of healthy women was reached in both groups. Small differences were observed between the two groups in the subscale role-physical and role-emotional, but 1-year after treatment these differences were minor and not clinically relevant. The most prevalent symptoms of the RSCL were tiredness, decreased sexual interest, painful muscles and sweating. During follow-up, 10% of all patients experienced 3 or 4 of these symptoms for at least 50% of the time. Only a lower educational level could distinguish these patients.

Shortly after high-dose chemotherapy, HRQoL was more affected than after conventional-dose chemotherapy. One year after randomization differences were negligible and only 10% of the patients experienced symptoms regularly. Patients with many symptoms after 5 years scored significantly lower on all SF-36 subscales at randomization and at the 11 measurement points thereafter compared with other patients. Eighty percent of patients with few symptoms at randomization reported few complaints after 5 years and half of all patients scoring many symptoms at randomization again reported many symptoms after 5 yeas. This indicates that having complaints before chemotherapy predicts a worse HRQoL outcome.

A frequently mentioned symptom by many patients in above study was fatigue. Other studies also found that many cancer survivors report fatigue after the completion of cancer treatment. Fatigue can be highly distressing to patients and is limiting the quality of life. A better understanding of long-term fatigue in cancer survivors is, therefore fundamental to the development of appropriate intervention strategies.

In **Chapter 3** fatigue was studied in a prospective longitudinal way. In breast cancer patients it was evaluated whether conventional or high-dose chemotherapy affected changes in fatigue, hemoglobin, mental health, muscle and joint pain, and menopausal status. We also evaluated whether fatigue was associated with these factors. Eight hundred four breast cancer patients were randomly assigned between high-dose and conventional-dose chemotherapy both followed by radiotherapy and tamoxifen. Fatigue was assessed using

vitality scale (score ≤ 46 defined as fatigue) and poor mental health using mental health scale (score ≤ 56 defined as poor mental health) both of SF-36. Muscle and joint pain were assessed with the Rotterdam Symptom Checklist. The SF-36, the RSCL and hemoglobin levels were assessed before and 1, 2 and 3 years after chemotherapy. Fatigue was reported in 20% of 430 evaluable disease free patients (202 conventional-dose, 228 high-dose) with at least a 3-year follow-up. Mean hemoglobin levels were lower following high-dose chemotherapy. Only 5% of patients experienced fatigue and anemia. In the 3 years after treatment, no significant differences in fatigue were found between conventional and high-dose chemotherapy and the norm population. Fatigue did not change over time. Sixteen percent of the patients in the present study experienced poor mental health at 3 years after therapy. Joint pain was observed in 20 % and muscle pain in 27 % of the patients at 3 years. Mental health score was the strongest fatigue predictor at all assessment moments. Menopausal status had no effect on fatigue. Linear mixed effect models showed that the higher the hemoglobin level ($P = .0006$) and mental health score ($P < .0001$), the less fatigue was experienced. Joint ($P < .0001$) and muscle pain ($P = .0283$) were associated with more fatigue.

In conclusion, we found that long-term fatigue occurs in 20 % of the women adjuvantly treated for breast cancer. Fatigue scores did not differ between the two treatment groups or from norm population scores and did not change over time. Anemia plays a small causative role in fatigue, but less than expected. The strongest relationship was found between fatigue and poor mental health.

Besides fatigue, patients with a history of breast cancer due to the occurrence menopause or hormonal treatment often report hot flashes. In **Chapter 4** an overview is given of the literature with regard the pathophysiologic mechanisms leading to hot flashes, the prevalence and severity of hot flashes in breast cancer patients, their influence on quality of life and the therapeutic options.

The underlying pathophysiologic mechanisms of vasomotor symptoms are poorly understood, but estrogen withdrawal is considered to be the instigator for hot flashes. The neurotransmitters serotonin and norepinephrine are both involved in central thermoregulation and seem to play a role in the induction of hot flashes as well. Breast cancer patients experience more frequent and more severe hot flashes than healthy postmenopausal women. This is mainly the result of systemic breast cancer treatment such as chemotherapy and endocrine therapy. Cytotoxic agents induce ovarian damage, which can become clinically manifest by the sudden onset of menopause. The abrupt and premature induction of menopause by chemotherapy may lead to exaggerated menopausal symptoms, including hot flashes.

Endocrine agents such as tamoxifen, aromatase inhibitors, and luteinizing hormone releasing hormone (LHRH) analogues are all used in the treatment of early or advanced breast cancer and hot flashes are a frequent side effect. The period over which endocrine therapy is administered has increased to several years and the rising number of treated patients makes the treatment of hot flashes more relevant as they may impair quality of life and may negatively influence adherence to endocrine treatment. Treatment with estrogens is very effective for the reduction of hot flashes, but is contraindicated in breast cancer patients because of the potential risk of tumor recurrence or the development of a new primary breast tumor. Several therapeutic options for hot flashes have been studied but none of them is as effective as estrogen. Clonidine and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine are two of the most studied and effective non-hormonal drugs.

Most studies evaluated non-hormonal drugs for the treatment of hot flashes in breast cancer patients for a maximum period of 4 weeks, this period is too short to evaluate aspects as side effects, quality of life and sexual functioning. It is also not known whether these drugs are effective if administered for a longer time period and what the spectrum of side effects is if used over a longer and more clinical relevant time period.

In **Chapter 5** we performed a prospective study comparing venlafaxine and clonidine for the treatment of hot flashes in breast cancer patients. The two drugs were compared in a double-blind, cross-over study, with regard to side effects, efficacy, quality of life and sexual functioning. Both drugs were administered for a period of 8 weeks. Sixty breast cancer patients ≤60 years and experiencing 14 or more hot flashes per week were randomized to 8 weeks of venlafaxine 75 mg once daily followed by a 2 weeks wash-out period, and 8 weeks of clonidine 0.05 mg twice daily or vice versa. Hot flash frequency and severity were recorded in a diary. Side effects, health related quality of life and sexuality were assessed using questionnaires.

Thirty patients started treatment with venlafaxine and 30 patients started with clonidine. Of the 60 patients, forty patients completed both 8 weeks treatment periods. Premature discontinuation occurred in 15 of the 59 patients during venlafaxine and in 5 out of 53 patients during clonidine ($P = .038$). Reasons for premature discontinuation were side effects in all but one patient, who initially on venlafaxine stopped study participation early due to cancer progression requiring chemotherapy. During the first 2 weeks of treatment, venlafaxine induced more toxicity, namely nausea, constipation, taste alteration and appetite loss than clonidine. At the end of the 8-week treatment periods less toxicity was reported, indicating that most side effects resolved with time

although women reported more appetite loss (24% vs 4%; $P = .03$), but less sleep disturbance (55% vs 75%; $P = .03$) on venlafaxine compared to clonidine.
The median reduction in hot flash score was 49% for venlafaxine and 55% for clonidine (ns). The patients that experienced a ≥50% reduction in hot flash score after 8 weeks of venlafaxine reported an improvement in several aspects of health related quality of life. The mean scores of the subscales mental health, physical functioning, social functioning, and role-physical showed a clinically meaningful improvement. Patients with a ≥50% reduction on clonidine demonstrated only an improved vitality score.
Only half of the patients was sexually active and no effects of venlafaxine or clonidine on sexual functioning in this group could be found. At study completion 33% of the patients chose to continue clonidine, 29% venlafaxine (ns), whereas 38% declined further treatment.
Summarized we found that side effects are the main reason for drug discontinuation, during the first weeks of treatment and occurred more often with venlafaxine. After 8 weeks however, both drugs are well tolerated. Venlafaxine and clonidine are equally, but moderately effective in hot flash reduction in breast cancer patients.

Endocrine treatment is based on the presence or absence of estrogen receptor and/or progesterone receptor status of the breast cancer cells. Drugs used for endocrine tumor treatment are targeted either directly at the estrogen receptor (tamoxifen) or at eliminating the estrogen production. The latter is achieved by inhibiting the conversion of androgens into estrogens (aromatase inhibitors) or by acting on the hypothalamic-pituitary axis (LHRH analogues). Another way of acting on the hypothalamic-pituitary axis is surgical ablation (surgical removal of the ovaries). Endocrine treatment plays an important role in the adjuvant and palliative treatment of breast cancer patients. The long-term impact of endocrine therapies is increasingly relevant, as patients are treated for years, the number of breast cancer survivors is increasing and more young women are treated with this modality.
Chapter 6 provides a literature-based overview of side effects of hormonal treatment in pre- and postmenopausal breast cancer patients both in the adjuvant and palliative setting and the influence on the HRQoL and sexuality.
There are several types of endocrine treatments available such as selective estrogen receptor modulators (SERMs), non-steroidal and steroidal aromatase inhibitors, pure ER-antagonists, progestins and luteinising hormone-releasing hormone (LHRH) agonists, which play an important role in breast cancer treatment. The long-term impact of endocrine therapies is increasingly relevant, as patients are treated for years, the number of breast cancer survivors is

increasing and more young women are treated with this modality. HRQoL data can assist in recommendations for future treatment. In the review relevant clinical studies were identified by using the Medline database, limited to literature in English from between 1977-2006. Side effect profiles of tamoxifen and aromatase inhibitors vary but no significant difference in overall HRQoL was observed. Looking at the balance between efficacy and side effects, the aromatase inhibitors seem to outperform tamoxifen. Tamoxifen increases the incidence of endometrial cancer. Fewer thromboembolic events occur during aromatase inhibitors than with tamoxifen. The incidence of muscle pain and stiffness, joint disorders, and bone fractures was highest during aromatase inhibitors. Although patients may experience a wide range of symptoms, there are only minor differences in HRQoL ratings and they are generally rated as "good". Further research should allow healthcare professionals to tailor their care even more specifically to patients' individual circumstances, providing better disease control while maintaining HRQoL.

The oldest endocrine drug for the treatment of breast cancer is tamoxifen, a non-steroidal anti-estrogen. As a consequence of its agonistics effects on the endometrium versus an antagonistic effect on the breast tumor an increased incidence of endometrial hyperplasia, polyps and 2-3 fold increased risk of endometrial adenocarcinoma and endometrial sarcoma have been described in tamoxifen using breast cancer patients.

In **Chapter 7.1** a case report of a postmenopausal breast cancer using tamoxifen is described which illustrates that tamoxifen can induce gynaecological changes that raise diagnostic problems. After 2 years of tamoxifen use this patient was referred with vaginal blood loss and a large pelvic mass. Transvaginal ultrasound (TVU) revealed an enlarged uterus with markedly increased endometrial thickness of 7-8 cm with a multicystic aspect. Because of persistent bleeding a total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Histology showed a large, benign endometrial polyp. A multicystic endometrium or benign polyps, such as found in our patient, are typical for chronic tamoxifen users, and may wrongly raise the impression of a malignancy.

In **Chapter 7.2** we investigated the influence of tamoxifen on the endometrium and the menstrual cycle in premenopausal breast cancer patients. Breast cancer patients using tamoxifen and 55 years of age or younger were investigated. The patients last menstrual period registered and the endometrial response measured by TVU every 6 months. Premenopausal status was defined as serum levels of estradiol (E_2) $\geq$0.10 nmol/L and follicle stimulating hormone (FSH) $\leq$30 IU/L. Patients with an endometrial response of >12 mm were offered an hysteroscopy and curettage.

A total of 241 TVU measurements were performed in 121 patients. Amenorrhea predicted menopausal status incorrectly in 85 of the 241 (35%) measurements in 47 patients. In 8 of the 47 premenopausal patients TVU showed an endometrial response of 12 of more mm (range15-29 mm). Histopathology revealed no malignancy in 6 of the 8 women with an increased endometrial thickness. No relation between estradiol levels and endometrial response was found.
In conclusion, tamoxifen leads to a disconnection between clinical and endocrinological menopause in breast cancer patients 55 years of age or younger. In premenopausal patients tamoxifen has a predominantly anti-estrogenic effect on the endometrium without a correlation between estradiol levels and endometrial response.

FUTURE PERSPECTIVES

Results of the study described in **Chapter 2** showed that shortly after high-dose chemotherapy, HRQoL was more affected than after conventional-dose chemotherapy. One year after randomization differences were negligible and only 10% of the patients experienced symptoms regularly. Patients with many symptoms after 5 years scored lower on all SF-36 subscales at randomization and at the 11 measurement points thereafter compared with other patients. Eighty percent of patients with few symptoms at randomization reported few complaints after 5 years and half of all patients scoring many symptoms at randomization again reported many symptoms after 5 years. This indicates that having complaints before chemotherapy predicts a worse HRQoL outcome. This finding might assist future studies that are aiming to support those patients that may especially benefit of it.

Many cancer survivors experience fatigue as a chronic health problem. It has been identified as one of the most common and distressing problem for people with cancer. Cancer related fatigue has great impact on patients' HRQoL while the processes underlying long-term fatigue in cancer patients are still unknown. In **Chapter 3** we describe our findings that long-term fatigue occurs in 20% of the women below the age of 56, adjuvantly treated for breast cancer. Fatigue scores did not differ between the two treatment groups or from norm population scores and did not change over time. Anemia played a small causative role in fatigue, but less than expected. The strongest relationship was found between fatigue and poor mental health. The use of recombinant human erythropoietin to treat anemia in cancer patients has received a lot of attention in the past to be considered as solution for fatigue. Our results illustrate that in

this group of patients only a very modest effect on fatigue is to be expected. This is even of more interest as recently concerns surrounding the use of erythropoietin to treat anemia in cancer patients have been raised. Two clinical studies reported a worse survival outcome in patients who received erythropoietin compared with patients who received placebo. These findings contrast with previous clinical studies, which showed no difference in survival for cancer patients who received erythropoiesis-stimulating agents. More recent preclincial data suggest that erythropoietin is an important angiogenic factor that regulates the induction of tumor cell-induced neovascularization and growth during tumorgenesis.

As there seems to be a strong correlation between fatigue and depression, studies early assessment of both fatigue and depression in patients with breast cancer could assist in timely support of these patients. Development of effective clinical strategies to manage fatigue continues to be a challenge for future research.

The problem of hot flashes in breast cancer patients will increase in the future because more patients will be treated for a longer periods of time. Patients reporting side effects are more likely to stop tamoxifen prematurely risking cancer recurrence. Therefore, the development of strategies to circumvent these side effects is important, as they may increase therapy adherence. With regard to alleviating hot flashes in breast cancer patients, there is no treatment yet as effective as estrogens (**Chapter 4**). Venlafaxine and clonidine are equally, but moderately effective in hot flashes reduction (**Chapter 5**). For that reason further studies should focus on finding non-hormonal treatment options with an increased efficacy in reducing hot flashes and limited side effects. Safety is a major concern in this respect and attention should be paid to potential stimulating effects on tumor cells. Recent evidence shows that selective serotonin-reuptake inhibitors (SSRIs) interfere with tamoxifen metabolism by inhibiting cytochrome P450 2D6 (CYP2D6). This results in lower concentrations of endoxifen, the most active tamoxifen metabolite. As a consequence, concomitant administration of tamoxifen and a SSRI is potentially harmful for the patient. As venlafaxine is a weak inhibitor of CYP2D6 and only slightly reduces plasma endoxifen levels, it is considered to be safe for the treatment of hot flashes in breast cancer patients. Nevertheless, in the search for other and more effective drugs for the reduction of hot flashes safety aspects should be kept in mind. Findings in **Chapter 7.2** underscore the relevance of a correct determination of menopausal status by assessing estradiol and FSH levels in these patients.

Side effect profiles of tamoxifen and aromatase inhibitors vary but no significant difference in overall HRQoL was observed (**Chapter 6**). The variation in side effects profiles provides however healthcare workers possibilities to tailor their care more specifically to patients' individual circumstances. This way they can offer the same or better disease control while maintaining HRQoL.