VOLUME 35 · NUMBER 29 · OCTOBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Fear of Cancer Recurrence in an Era of Personalized Medicine

Belinda Thewes, Olga Husson, Hanneke Poort, Jose A.E. Custers, *Radboud University Medical Center, Nijmegen, the Netherlands*
Phyllis N. Butow, *The University of Sydney, Sydney, New South Wales, Australia*
Sue-Anne McLachlan, *St Vincent's Hospital, Melbourne, and The University of Melbourne, Parkville, Victoria, Australia*
Judith B. Prins, *Radboud University Medical Center, Nijmegen, the Netherlands*

Cancer mortality rates have fallen and the number of survivors of cancer has increased steadily since the 1990s.[1,2] Recently, there have been major survival advances for some previously deadly cancers as a result of the increased understanding of the molecular, genetic, and immunologic basis of cancer and the introduction of personalized medicines; however, novel therapies are raising questions about the optimal duration of therapy and follow-up and changing how the risk of recurrence is communicated. Although considerable attention has been given to studying the survival impact of novel therapies, to date, little attention has been given to understanding their effect on psychological factors, such as the fear of cancer recurrence (FCR).

FCR has recently been defined as "fear, worry, or concern relating to the possibility that cancer will come back or progress,"[3(p3266)] and it is one of the most common unmet needs for help among survivors.[4] Mild or transitory FCR is normal and can motivate appropriate health behaviors[5,6]; however, pathologic FCR is characterized by chronic worry, excessive body checking and/or seeking of medical reassurance, avoidance of cancer reminders, intrusive thoughts and images about recurrence, and future planning difficulties.[4,7-10] Moderate to high levels of FCR affect, on average, 49% of survivors of cancer and up to 70% of patients in vulnerable groups.[4,7,11] Approximately 7% of patients experience severe and disabling FCR.[4] Patients with high FCR report distress, poorer health-related quality-of-life (HRQOL), functional impairments, and stress symptoms.[4,8,11] Younger age and physical symptoms are the most consistent predictors of high FCR.[4,8] To date, there is inconsistent evidence for a relationship between treatment type and objective indices of illness severity[4,8,12]; however, most studies include patients who receive conventional therapies.

Theoretical models of FCR emphasize the triggering role of medical investigations and exposure to reminders of cancers[6,10,13] as well as the maintaining role of frequent checking, seeking reassurance, and beliefs about disease chronicity.[6,10] Whereas individual factors—for example, psychological vulnerability, and cognitive style—play a role in the development and maintenance of high FCR,[6,10,13] iatrogenic factors that are associated with novel cancer treatments may also contribute to FCR. More specifically, the extended treatment duration and the monitoring for signs of recurrence associated with novel therapies, as well as the increased availability of information to predict individual treatment response or risk of recurrence, may contribute to growing numbers of patients being vulnerable to FCR in future decades. This commentary illustrates these issues, with examples drawn from the introduction of targeted tyrosine kinase inhibitors (TKIs), tumor-specific DNA profiling, and immunotherapy.

TKIs were the poster child of targeted therapies because of the dramatically improved survival after their introduction in the treatment of chronic myeloid leukemia (CML)[14] and GI stromal tumors (GISTs).[15,16] Coupled with herceptin, TKIs have the longest history of use as novel targeted therapies and, to date, the most data available about how best to apply them in clinical practice. In the treatment of advanced cancer and CML, oral TKIs are administered daily (or twice daily) indefinitely until patients experience intolerance or progression. In localized GISTs, the recommended duration of TKI therapy (imatinib) is a minimum of 36 months,[17,18] and in localized renal cell carcinoma, sunitinib is administered for 12 months.[19] Although chemotherapies also require regular follow-up, with the frequency dependent on risk, they are rarely administered for such extended periods of time because of toxicity. Extended treatment regimens may be one reason that patients with GISTs and CML are vulnerable to FCR and other psychological concerns that compromise quality of life.[20,21] Interviews of health care providers also suggest that fear of progression is more prominent in patients with CML who need to switch to another TKI after experiencing treatment failure.[22] A recent trial has demonstrated that imatinib can be safely discontinued and restarted in patients with CML with a sustained molecular response[23]; however, approximately one half (49%) of patients with CML would not be willing to discontinue TKIs because of fear of losing therapeutic response.[24]

Monitoring for signs of recurrence or progression during TKI therapy takes place regularly—approximately quarterly. There are emerging guidelines for optimal follow-up after treatment with TKIs for patients with GISTs[25,26]; however, no consensus guidelines are available, so variation between clinicians is common. Uncertainty concerning optimal follow-up may further contribute to FCR. Although TKIs are generally associated with fewer adverse effects and better HRQOL than chemotherapy, relying on HRQOL alone as an indicator of functioning may obscure FCR. For example, among 86 people who were treated for GISTs, the majority reported good HRQOL, yet more than one half (52%) of patients reported levels of FCR above a validated cutoff for high FCR.[27]

Thus, it is important to consider FCR measures as a secondary outcome in clinical trials.

Additional genomic data may strengthen the ability to stratify the risk of recurrence or progression in patients with GISTs and to inform optimal monitoring and treatment duration—for example, mutational analyses for KIT and loss of CDKN2A or plasma sequencing of KIT/PDGFRA.[28] Such information may help reduce unnecessary follow-up visits and treatment burden in low-risk patients, but the psychological impact of these test results are currently nonvalidated and potentially meaningless, and the frequency of follow-up is untested but warrants investigation. Targeted therapies are evolving quickly, with newer agents rapidly entering clinical practice—for example, in a subset of patients with non–small-cell lung cancer with specific molecular abnormalities (eg, epithelial growth factor receptor mutation and anaplastic lymphoma kinase positive). However, uncertainty remains about the durability of treatment effect, and, in the absence of a better understanding of optimal follow-up, there is frequent and extended monitoring for recurrence or progression. This uncertain context, with frequent investigations over a protracted period of time, may exacerbate FCR.

The introduction of tumor-specific DNA profiling has also brought about new challenges with regard to FCR. Furthermore, patient and tumor characteristics, rather than family history, drive access to germline mutation testing in patients with cancer.[29] Growing numbers of patients will be presented with a complex array of genomic information and, in some cases, the option to forgo standard treatments on the basis of low-risk genomic characterization. To date, there is relatively little research on the psychological effect of treatment-focused germline or somatic mutation testing,[29-32] or how the results of genomic profiling for the risk of recurrence are optimally communicated. Existing data are qualitative or semiqualitative and include patients with breast, colorectal, and lung cancer and melanoma. Results suggest that somatic testing is generally highly acceptable because it is perceived to provide access to targeted therapies[30,31]; however, a negative result may diminish hope because of the probability of having fewer treatment options.[30] Positive results of germline mutation tests may result in adverse psychological consequences, especially for those with no family history.[29] Despite the availability of a growing number of genomic assays to predict risk of cancer recurrence—for example, Mammaprint, Oncotype DX, EndoPredict, PAM50, Mammostrat—no studies have investigated the relationship between FCR and a patient being informed of having a high-genomic risk of recurrence profile or forgoing standard therapy on the basis of having a low-risk genomic profile.

In the MINDACT (Microarray In Node-Negative and 1-3 Node Positive Disease May Avoid Chemotherapy) trial, women with early breast cancer with high clinical risk but low genomic risk of recurrence (HC-LGR) who were randomly assigned to forgo chemotherapy on the basis of the 70-gene signature test (Mammaprint) had a 1.5%-lower chance of 5-year recurrence-free survival (94.7%) compared with those who received chemotherapy (96.2%). The confidence interval for HC-LGR patients did not include a prespecified noninferiority boundary, which suggests that HC-LGR patients can safely forgo chemotherapy; however, most patients with early breast cancer will accept chemotherapy for small survival gains ($\leq$ 1%).[33,34] Whether HC-LGR patients are willing to forgo chemotherapy outside of a clinical trial is not known. The psychological impact of forgoing chemotherapy was not investigated in MINDACT. One could speculate that HRQOL among HC-LGR patients who were randomly assigned to forgo chemotherapy would be better compared with those who received chemotherapy because of the lower adverse effect burden; however, higher levels of FCR may be observed as a result of survival gain tradeoffs. Tumor-specific DNA profiling is now being extended to other cancer types—for example, the sequencing of DNA from colorectal cancers has identified recurrently somatically mutated genes.[35,36] These tumor-specific DNA mutations can be detected in the cell-free component of peripheral blood (circulating tumor DNA) in most patients with metastatic cancer, which allows for future noninvasive molecular tumor characterization.[36] The growth of DNA-specific mutation testing is likely to extend issues concerning FCR and pretreatment genetic profiling, observed in MINDACT, to other cancer types.

Immunotherapy is another major paradigm shift in oncology in which research has taken off at an incredible pace. New immunotherapies that block programmed death 1 and programmed death-ligand 1 immune checkpoints extend survival from months to years for a subset of patients with advanced melanoma.[37] Durable responses observed after ipilimumab therapy in selected patients with advanced melanoma have caused some to question whether long-term remission might represent cure[38]; however, more than one half of patients currently selected for immunotherapy either do not benefit or only experience a short-lived response.[39] Biomarkers to predict which patients benefit and experience durable responses after immunotherapy are currently being investigated. Despite the efficacy, there is a currently a lack of HRQOL data on immunotherapies and insufficient evidence regarding their optimal duration. To date, little is known about which patients can safely discontinue therapy. Despite the relatively low toxicity,[40,41] the high cost of immunotherapy will generate answers to these questions but, until then, FCR is likely to be a prominent concern among those who receive immunotherapy because of the prolonged survival in a previously fatal cancer, combined with the uncertainties that surround treatment response and duration of treatment. Over the past year, the US Food and Drug Administration approved five new uses for immune checkpoint inhibitors in advanced lung, head and neck, bladder, and kidney cancers and Hodgkin lymphoma; therefore, these issues will soon be extended to other groups.[39]

CLINICAL IMPLICATIONS

Weighing adverse effects with uncertain benefits has always been part of treatment decision making by patients with cancer and physicians; however, the addition of personalized molecular and genetic tumor characteristics to guide treatment decision making introduces new challenges with regard to the communication of risk.

FCR is an emerging research topic and validated instruments are now available to assess FCR (Appendix Table A1, online only),[42] including some that have been specifically developed for clinical trials.[43] Whereas some clinical trials of novel therapeutic agents and biomarkers include HRQOL substudies—for example, the ECOG-COMET clinical trial (ClinicalTrial.gov identifier: NCT02823652)—none, to date, have included questionnaires

that assess FCR. Personalized medicine may demand an even greater tolerance of uncertainty,[44] yet FCR research is largely restricted to patients who have been treated with conventional cancer therapies and with prevalent forms of cancer.[4] We recommend that FCR be considered a secondary outcome in future trials of targeted therapies, tumor-specific DNA profiling, and immunotherapies because it can help identify late effects associated with these treatments and alert clinicians to the need to offer preventive or therapeutic measures to reduce the impact of FCR in contexts where it is likely to occur. FCR is also pertinent to studies that investigate the optimal follow-up frequency as well as decision making or doctor–patient communication concerning the risk of recurrence in the context of personalized medicine.[45]

Several randomized controlled trials of psychological interventions for severe and highly disabling FCR are underway or nearing completion,[46-50] and one randomized controlled trial comparing two group therapies is completed.[51] Novel electronic-health treatment approaches for FCR are also being evaluated.[47,52] The majority of psychological interventions for FCR are based on cognitive behavior therapy and address coping with intrusive thoughts and images, reducing safety-seeking behaviors (eg, excessive body checking or excessive reassurance seeking), and promoting patients' abilities to make future plans. Pilot data and first trial results[50,53,54] suggest that FCR interventions are effective, and efforts to disseminate and implement them in routine care are now underway.

Although it is unlikely that patients would choose to forgo life-prolonging treatments because of potential FCR, understanding FCR among those who receive novel therapies and tumor-specific DNA profiling is nevertheless important. Such understanding will enable clinicians to understand the psychological late effects of new treatments and tests and discern the advantages and disadvantages of those approaches from the patient's perspective. It can also serve to improve doctor–patient communication concerning FCR. An awareness of the prevalence, predictors, and mediators of FCR in those who receive personalized medicine might be used to develop psychoeducation that can prevent FCR in the most vulnerable patients. We encourage clinicians to be aware of FCR and to investigate the potential effects of chronic treatments, intensive monitoring, and the provision of information that concerns the personalized risk of disease recurrence. Improved understanding of FCR will also allow clinicians to identify patients who may benefit from new evidence-based psychological treatments for high FCR.[46,47]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Ryerson AB, Eheman CR, Altekruse SF, et al: Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 122:1312-1337, 2016

2. International Agency for Research on Cancer: World cancer report 2014. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014

3. Lebel S, Ozakinci G, Humphris G, et al: From normal response to clinical problem: Definition and clinical features of fear of cancer recurrence. Support Care Cancer 24:3265-3268, 2016

4. Simard S, Thewes B, Humphris G, et al: Fear of cancer recurrence in adult cancer survivors: A systematic review of quantitative studies. J Cancer Surviv 7: 300-322, 2013

5. Herschbach P, Dinkel A: Fear of progression, in Goerling U (ed): Psycho-oncology, Berlin, Germany, Springer, pp 11-29

6. Lee-Jones C, Humphris G, Dixon R, et al: Fear of cancer recurrence—A literature review and proposed cognitive formulation to explain exacerbation of recurrence fears. Psychooncology 6:95-105, 1997

7. Thewes B, Butow P, Bell ML, et al: Fear of cancer recurrence in young women with a history of early-stage breast cancer: A cross-sectional study of prevalence and association with health behaviours. Support Care Cancer 20: 2651-2659, 2012

8. Crist JV, Grunfeld EA: Factors reported to influence fear of recurrence in cancer patients: A systematic review. Psychooncology 22:978-986, 2013

9. Lebel S, Tomei C, Feldstain A, et al: Does fear of cancer recurrence predict cancer survivors' health care use? Support Care Cancer 21:901-906, 2013

10. Custers JA, Gielissen MF, de Wilt JH, et al: Towards an evidence-based model of fear of cancer recurrence for breast cancer survivors. J Cancer Surviv 11: 41-47, 2017

11. Koch L, Bertram H, Eberle A, et al: Fear of recurrence in long-term breast cancer survivors-still an issue. Results on prevalence, determinants, and the association with quality of life and depression from the cancer survivorship—A multi-regional population-based study. Psychooncology 23: 547-554, 2014

12. Yang Y, Cameron J, Humphris G: The relationship between cancer patient's fear of recurrence and radiotherapy: A systematic review and meta-analysis. Psychooncol 10.1002/pon.4224 [epub ahead of print on July 15, 2016]

13. Fardell JE, Thewes B, Turner J, et al: Fear of cancer recurrence: A theoretical review and novel cognitive processing formulation. J Cancer Surviv 10:663-673, 2016

14. Druker BJ, Talpaz M, Resta DJ, et al: Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031-1037, 2001

15. van Oosterom AT, Judson I, Verweij J, et al: Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: A phase I study. Lancet 358:1421-1423, 2001

16. Blay JY: A decade of tyrosine kinase inhibitor therapy: Historical and current perspectives on targeted therapy for GIST. Cancer Treat Rev 37: 373-384, 2011

17. Artinyan A, Kim J, Soriano P, et al: Metastatic gastrointestinal stromal tumors in the era of imatinib: Improved survival and elimination of socioeconomic survival disparities. Cancer Epidemiol Biomarkers Prev 17:2194-2201, 2008

18. Casali PG: Successes and limitations of targeted cancer therapy in gastrointestinal stromal tumors. Prog Tumor Res 41:51-61, 2014

19. Ravaud A, Motzer RJ, Pandha HS, et al: Adjuvant sunitinib in high-risk renal cell carcinoma after nephrectomy. N Engl J Med 375:2246-2254, 2016

20. Efficace F, Breccia M, Cottone F, et al: Psychological well-being and social support in chronic myeloid leukemia patients receiving lifelong targeted therapies. Support Care Cancer 24:4887-4894, 2016

21. Phillips KM, Pinilla-Ibarz J, Sotomayor E, et al: Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: A controlled comparison. Support Care Cancer 21:1097-1103, 2013

22. Poort H, Meade CD, Knoop H, et al: Adapting an evidence-based intervention to address targeted therapy-related fatigue in chronic myeloid leukemia patients. Cancer Nurs [epub ahead of print on November 8, 2016]

23. Etienne G, Guilhot J, Rea D, et al: Long-term follow-up of the French Stop Imatinib (STIM1) study in patients with chronic myeloid leukemia. J Clin Oncol 35: 298-305, 2017

24. Breccia M, Efficace F, Sica S, et al: Adherence and future discontinuation of tyrosine kinase inhibitors in chronic phase chronic myeloid leukemia. A patient-based survey on 1133 patients. Leuk Res 39:1055-1059, 2015

25. von Mehren M, Randall RL, Benjamin RS, et al: Gastrointestinal stromal tumors, version 2.2014. J Natl Compr Canc Netw 12:853-862, 2014

26. ESMO/European Sarcoma Network Working Group: Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 25:iii21-iii26, 2014 (suppl 3)

27. Custers JA, Tielen R, Prins JB, et al: Fear of progression in patients with gastrointestinal stromal tumors (GIST): Is extended lifetime related to the Sword of Damocles? Acta Oncol 54:1202-1208, 2015

28. Corless CL, Ballman KV, Antonescu CR, et al: Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: The ACOSOG Z9001 trial. J Clin Oncol 32:1563-1570, 2014

29. Meiser B, Quinn VF, Gleeson M, et al: When knowledge of a heritable gene mutation comes out of the blue: Treatment-focused genetic testing in women newly diagnosed with breast cancer. Eur J Hum Genet 24:1517-1523, 2016

30. Liang R, Meiser B, Smith S, et al: Advanced cancer patients' attitudes towards, and experiences with, screening for somatic mutations in tumours: A qualitative study. Eur J Cancer Care (Engl) [epub ahead of print on October 11, 2016]

31. Yusuf RA, Rogith D, Hovick SRA, et al: Attitudes toward molecular testing for personalized cancer therapy. Cancer 121:243-250, 2015

32. Gray SW, Hicks-Courant K, Lathan CS, et al: Attitudes of patients with cancer about personalized medicine and somatic genetic testing. J Oncol Pract 8: 329-335, 2, 335, 2012

33. Duric V, Stockler M: Patients' preferences for adjuvant chemotherapy in early breast cancer: A review of what makes it worthwhile. Lancet Oncol 2: 691-697, 2001

34. Duric VM, Stockler MR, Heritier S, et al: Patients' preferences for adjuvant chemotherapy in early breast cancer: What makes AC and CMF worthwhile now? Ann Oncol 16:1786-1794, 2005

35. Thomas RK, Baker AC, Debiasi RM, et al: High-throughput oncogene mutation profiling in human cancer. Nat Genet 39:347-351, 2007 [Erratum: Nat Genet 39:567, 2007]

36. Wood LD, Parsons DW, Jones S, et al: The genomic landscapes of human breast and colorectal cancers. Science 318:1108-1113, 2007

37. Luke JJ, Ott PA: PD-1 pathway inhibitors: The next generation of immunotherapy for advanced melanoma. Oncotarget 6:3479-3492, 2015

38. Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-723, 2010

39. Burstein HJ, Krilov L, Aragon-Ching JB, et al: Clinical cancer advances 2017: Annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 35:1341-1367, 2017

40. Topalian SL, Hodi FS, Brahmer JR, et al: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443-2454, 2012

41. Weber JS, Hodi FS, Wolchok JD, et al: Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. J Clin Oncol 35: 785-792, 2017

42. Thewes B, Butow P, Zachariae R, et al: Fear of cancer recurrence: A systematic literature review of self-report measures. Psychooncology 21:571-587, 2012

43. Curran D, van Dongen JP, Aaronson NK, et al: Quality of life of early-stage breast cancer patients treated with radical mastectomy or breast-conserving procedures: Results of EORTC Trial 10801. The European Organization for Research and Treatment of Cancer (EORTC), Breast Cancer Co-operative Group (BCCG). Eur J Cancer 34:307-314, 1998

44. Hunter DJ: Uncertainty in the era of precision medicine. N Engl J Med 375: 711-713, 2016

45. Thewes B, Prins JB, Friedlander M: 70-gene signature in early-stage breast cancer. N Engl J Med 375:2199-2201, 2016

46. Butow PN, Bell ML, Smith AB, et al: Conquer fear: Protocol of a randomised controlled trial of a psychological intervention to reduce fear of cancer recurrence. BMC Cancer 13:201, 2013

47. van de Wal MA, Gielissen MF, Servaes P, et al: Study protocol of the SWORD-study: A randomised controlled trial comparing combined online and face-to-face cognitive behaviour therapy versus treatment as usual in managing fear of cancer recurrence. BMC Psychol 3:12, 2015

48. Maheu C, Lebel S, Courbasson C, et al: Protocol of a randomized controlled trial of the fear of recurrence therapy (FORT) intervention for women with breast or gynecological cancer. BMC Cancer 16:291, 2016

49. Lebel S, Maheu C, Lefebvre M, et al: Addressing fear of cancer recurrence among women with cancer: A feasibility and preliminary outcome study. J Cancer Surviv 8:485-496, 2014

50. van de Wal M, Thewes B, Gielissen M, et al: Efficacy of blended cognitive behavior therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD study, a randomized controlled trial. J Clin Oncol 10.1200/JCO.2016.70.5301 [epub ahead of print on May 4, 2017]

51. Herschbach P, Berg P, Waadt S, et al: Group psychotherapy of dysfunctional fear of progression in patients with chronic arthritis or cancer. Psychother Psychosom 79:31-38, 2010

52. van Helmondt SJ, van der Lee ML, de Vries J: Study protocol of the CAREST-trial: A randomised controlled trial on the (cost-) effectiveness of a CBT-based online self-help training for fear of cancer recurrence in women with curatively treated breast cancer. BMC Cancer 16:527, 2016

53. Smith A, Thewes B, Turner J, et al: Pilot of a theoretically grounded psychologist-delivered intervention for fear of cancer recurrence (Conquer Fear). Psychooncology 24:967-970, 2015

54. Maheu C, Lebel S, Tomei C, et al: Breast and ovarian cancer survivors' experience of participating in a cognitive-existential group intervention addressing fear of cancer recurrence. Eur J Oncol Nurs 19:433-440, 2015

DOI: https://doi.org/10.1200/JCO.2017.72.8212; published at jco.org on July 19, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Fear of Cancer Recurrence in an Era of Personalized Medicine

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Belinda Thewes
No relationship to disclose

Olga Husson
No relationship to disclose

Hanneke Poort
No relationship to disclose

Jose A.E. Custers
No relationship to disclose

Phyllis N. Butow
No relationship to disclose

Sue-Anne McLachlan
No relationship to disclose

Judith B. Prins
No relationship to disclose

Appendix

Table A1. Overview of FCR Questionnaires

Study	Name of Scale	No. of Items	Intended Population	Country of Development	Subscales/Item Domains
FCR Subscales of HRQOL or Other Psychosocial Questionnaires					
Kiebert, et al: Eur J Surg 159:601-607, 1993	FRS subscale	3	Mixed	Netherlands	Insecurity about health Frequency of FCR Belief in cure
Curran et al[43]	EORTC Recurrence Subscale of HRQOL scaled developed for EORTC 10801	3	Breast cancer. Suitable for patients with mixed cancers	International	Frequency of FCR Belief in cure Health worry
Melia, et al: Arch Ophthalmol 121: 1010-1020, 2003	Concern About Recurrence Subscale of the Collaborative Ocular Melanoma Study–Quality of Life Scale	3	Ocular melanoma	United States Canada	Frequency of FCR Degree of distress Perceived risk
Roth, et al: Cancer 97: 2910-2918, 2003, and Roth, et al: Psychosomatics 47:340-347, 2006	Fear of Recurrence Subscale of the Memorial Anxiety Scale for Prostate Cancer	4	Prostate	United States	Impact on future planning Impact on enjoyment Worry about progression/ recurrence General nervousness
Avis, et al: Health Qual Life Outcomes 4:92, 2006	Distress-Recurrence Subscale of the Quality of Life in Adult Cancer Survivors Scale	4	Mixed; long-term survivors	United States	Worry about death Worry about recurrence FCR triggered by pain Preoccupation with FCR
Zhao, et al: J Pain Symptom Manage 37: 676-686, 2009	Fear of Recurrence Subscale of the Cancer Problems in Living Scale	4	Mixed	United States	Degree of FCR Concern about recurrence Preoccupation with illness Fear about the future
Brief Stand-Alone FCR Questionnaires (2-10 items)					
Easterling, et al: J Appl Psychol 74:787-796, 1989	Cancer Worry Scale (A)	3	Breast cancer, suitable for patients with mixed cancers	United States	Frequency of FCR Intrusions Distress caused by FCR
Lasry, et al: Cancer 69: 2111-2115, 1992	Fear of Recurrence Index	2	Breast cancer, suitable for patients with mixed cancers	Canada	Patient intensity of FCR Carer intensity of FCR Worry about health
Greenberg, et al: Cancer 80:1936-1944, 1997	Fear of Relapse/Recurrence Scale	5	Hematologic, suitable for patients with mixed cancers	United States	Inability to plan for future Perceived risk of recurrence Impact of FCR Intensity of FCR Belief in cure
Rabin, et al: Health Psychol 23:407-412, 2004	FRS (A)	4	Breast cancer	United States	Frequency of FCR Emotional impact Functional impact Concern about FCR
Deimling, et al: Psychooncology 15:143-159, 2006	Cancer-Related Worries Scale	4	Mixed	United States	Concern about FCR Worry about future tests Worry about recurrence Worry about other forms of cancer

(continued on following page)

Table A1. Overview of FCR Questionnaires (continued)

Study	Name of Scale	No. of Items	Intended Population	Country of Development	Subscales/Item Domains
Gotay, et al: Health Qual Life Outcomes 5:15, 2007	Assessment of Survivor Concerns	5	Mixed	United States	Subscales 1. Cancer worry Recurrence New diagnosis Future tests 2. Health worry Death General health
Cameron, et al: Psychooncology 16:171-180, 2007	Cancer Worry Scale (B)	2	Breast cancer	United States	Frequency FCR Concern about recurrence
Diefenbach, et al: Psychol Health Med 13:146-161, 2008	Worry About Prostate Cancer Scale	2	Prostate cancer	United States	Worry about recurrence Worry about cancer spread
Hodges, et al: Psychooncology 18:841-848, 2009	Worry of Cancer Scale–Revised	2	Head and neck cancer, suitable for patients with mixed cancers Patients and carer version	United Kingdom	Frequency of FCR Degree of intrusiveness of FCR
Franssen, et al: Psychooncology 18: 1199-1207, 2009	FRS (B)	3	Esophageal cancer, suitable for mixed cancers	Netherlands	Frequency Belief in cure Fear of death
Simard, et al: Support Care Cancer 17:241-251, 2009	FCR Inventory- Severity Subscale (short form)	9	Mixed cancers	Canada	Frequency of FCR worry Frequency of FCR fear Belief FCR is normal Frequency of FCR intrusive thoughts/ images Perceived risk of recurrence Frequency of FCR Amount of time spent on FCR Duration of FCR
Thewes, et al: Psychooncology 21:571-587, 2012	Concerns About Recurrence Questionnairre	5	Breast cancer	Australia and Denmark	Frequency Degree of intrusion Degree of distress Perceived risk of recurrence Perceived risk (relative to others)
Custers, et al: Cancer Nurs 37:E44-E50, 2014	Cancer Worry Scale	8	Mixed cancers	Netherlands	Frequency of FCR (thoughts) Impact on mood Impact on daily life Degree of concern Frequency of FCR (worry) Perceive degree of problem Frequency of cancer worry for family Concern about surgery
Longer FCR Questionnaires (≥ 10 items)					
Northouse: Cancer Nurs 4: 213-220, 1981	Fear of Recurrence Questionnaire	22 items Patient and carer versions 6-item short form (Standton, et al: Psychooncology 11: 93-102, 2002)	Breast, suitable for mixed cancers	United States	No subscales. Item domains: Health worry Uncertainty Triggers Concerns of significant others Impact on future Attitudes toward future

(continued on following page)

Table A1. Overview of FCR Questionnaires (continued)

Study	Name of Scale	No. of Items	Intended Population	Country of Development	Subscales/Item Domains
Vickberg: Ann Behav Med 25:16-24, 2003	Concerns About Recurrence Scale	30 items	Breast	United States	Subscales 1. Overall fear 2. Health worries 3. Womanhood worries 4. Role worries 5. Death worries
Herschbach, et al: J Psychosom Res 58:505-511, 2005	Fear of Progression Questionnaire	43 items 12-item short form available (Mehnert, et al: Z Psychosom Med Psychother 52:274-288, 2006)	Patients with chronic illness, including mixed cancers, diabetes mellitus, rheumatic diseases	Germany	Subscales 1. Affective reactions 2. Partner and family 3. Occupation 4. Loss of autonomy 5. Coping with Anxiety
Simard, et al: Support Care Cancer 17:241-251, 2009	FCR Inventory	42 items 9-item short form available (see above)	Mixed	Canada	Subscales 1. Triggers 2. Severity 3. Psychological distress 4. Coping strategies 5. Functioning impairment 6. Insight 7. Reassurance

NOTE. For detailed summary, including the psychometric properties of available measures, consult the systematic review of FCR measures by Thewes, et al.[42]
Abbreviations: FCR, fear of cancer recurrence; FRS, fear of recurrence scale; HRQOL, health-related quality of life.