THE FOLLOW-UP IN BREAST CANCER PATIENTS

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June 6th - 7th, 2014
Palazzo Vermexio - Siracusa, Italy
FOLLOW UP

Periodic check up to detect potential recurrence of disease at early stage

OBJECTIVES : EARLY DETECTION

- Second tumors, ipsilateral or controlateral
- Local recurrences of disease
- Distant metastases

  to plan a timely and effective treatment, to improve the prognosis and to avoid severe complications;

- Potential psychological and rehabilitation needs to improve QoL
Cancer Survivors in US

<table>
<thead>
<tr>
<th>Year</th>
<th>Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971</td>
<td>3</td>
</tr>
<tr>
<td>2001</td>
<td>9.8</td>
</tr>
<tr>
<td>2007</td>
<td>12</td>
</tr>
<tr>
<td>2022</td>
<td>18</td>
</tr>
</tbody>
</table>

Cancer survivors USA 2007

- Female breast: 23%
- Prostate: 19%
- Colorectal: 17%
- Gynecologic: 10%
- Genitourinary: 9%
- Hematologic: 7%
- Melanoma: 6%
- Lung: 6%
- Other: 3%
Breast cancer survival

- 84% Stage 1
- 71% Stage 2
- 48% Stage 3
- 18% Stage 4

Graph showing survival rates over time for different stages of breast cancer.
Impact of Follow-up Testing on Survival and Health-Related Quality of Life In Breast Cancer Patients

The GIVIO Investigators

Setting: 26 Italian centers
Population: 1320 patients, age < 70 ys, Early breast carcinoma (stage I-III)

Clinical follow up
- Physical exam
- Mammography

Intensive follow up
- Physical exam
- Mammography
- Chest X-ray
- Bone scan

Table:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive, No. (%)</th>
<th>Control, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>55 (8)</td>
<td>57 (9)</td>
</tr>
<tr>
<td>40-49</td>
<td>184 (28)</td>
<td>194 (29)</td>
</tr>
<tr>
<td>50-59</td>
<td>218 (33)</td>
<td>205 (31)</td>
</tr>
<tr>
<td>≥60</td>
<td>198 (30)</td>
<td>209 (31)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre or peri</td>
<td>266 (41)</td>
<td>286 (43)</td>
</tr>
<tr>
<td>Post</td>
<td>387 (59)</td>
<td>378 (57)</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>365 (56)</td>
<td>374 (56)</td>
</tr>
<tr>
<td>Node positive</td>
<td>290 (44)</td>
<td>291 (44)</td>
</tr>
<tr>
<td>Pathological tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1</td>
<td>322 (49)</td>
<td>335 (51)</td>
</tr>
<tr>
<td>pT2</td>
<td>311 (48)</td>
<td>296 (45)</td>
</tr>
<tr>
<td>pT3</td>
<td>17 (3)</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (≥10 fmol)</td>
<td>359 (55)</td>
<td>383 (58)</td>
</tr>
<tr>
<td>Negative (0-9 fmol)</td>
<td>150 (23)</td>
<td>137 (21)</td>
</tr>
<tr>
<td>Unknown</td>
<td>146 (22)</td>
<td>145 (22)</td>
</tr>
</tbody>
</table>

RESULTS

At median follow up of 71 months: **no differences in OS:**
• 132 deaths (20%) in intensive vs 122 deaths (18%) in control group
  (Odds ratio=1.12; 95%CI=0.87 to 1.43)

**No differences in distant metastasis-free survival.**
Mean time to detection of distant M+: 53 vs 54 mos
Anticipation attributable to intensive follow-up: **less than 1 month**

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RESULTS

Impact on Health-Related Quality of Life and Preferences of Type of Care

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive</th>
<th>Control</th>
<th>Intensive</th>
<th>Control</th>
<th>Intensive</th>
<th>Control</th>
<th>Intensive</th>
<th>Control</th>
<th>Intensive</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality-of-life perception</td>
<td>63.6</td>
<td>65.2</td>
<td>65.6</td>
<td>66.6</td>
<td>66.6</td>
<td>66.8</td>
<td>68.9</td>
<td>70.6</td>
<td>68.6</td>
<td>68.9</td>
</tr>
<tr>
<td>Overall health perception</td>
<td>66.4</td>
<td>65.4</td>
<td>66.2</td>
<td>67.6</td>
<td>67.6</td>
<td>68.2</td>
<td>68.6</td>
<td>68.9</td>
<td>70.3</td>
<td>71.4</td>
</tr>
<tr>
<td>Body image</td>
<td>62.9</td>
<td>63.5</td>
<td>66.3</td>
<td>65.5</td>
<td>69.4</td>
<td>68.5</td>
<td>70.3</td>
<td>71.4</td>
<td>51.1</td>
<td>53.4</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>46.6</td>
<td>47.4</td>
<td>47.9</td>
<td>48.6</td>
<td>55.9</td>
<td>58.0</td>
<td>70.3</td>
<td>71.4</td>
<td>51.1</td>
<td>53.4</td>
</tr>
<tr>
<td>Social functioning</td>
<td>84.2</td>
<td>83.4</td>
<td>83.0</td>
<td>84.6</td>
<td>81.7</td>
<td>84.9</td>
<td>84.1</td>
<td>84.2</td>
<td>84.1</td>
<td>84.2</td>
</tr>
<tr>
<td>Symptoms</td>
<td>62.6</td>
<td>63.3</td>
<td>66.7</td>
<td>66.0</td>
<td>68.9</td>
<td>68.8</td>
<td>70.2</td>
<td>70.4</td>
<td>63.6</td>
<td>63.8</td>
</tr>
<tr>
<td>Satisfaction with care</td>
<td>63.4</td>
<td>64.5</td>
<td>63.6</td>
<td>64.7</td>
<td>62.8</td>
<td>63.8</td>
<td>63.6</td>
<td>63.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Type of follow up does not affect** the dimensions of health-related quality of life.

When asked about preferences for follow up, 70% said “**they wanted to be seen frequently by a physician and undergo diagnostic tests**”. This preference was not affected by whether the patient was assigned to the intensive or minimalist follow up regimen.
CA 15.3 IN THE FOLLOW UP OF LOCALIZED BC: A PROSPECTIVE STUDY

Patients: 243 localised BC
Methods: Ca 15-3 every 6 mos

Results:
Ca 15-3 is specific, but not sensitive to indicate relapse earlier than other methods. The positive predictive value remained poor. Ca 15.3 is not suitable alone for BC follow-up

<table>
<thead>
<tr>
<th>Ca 15-3 elevated</th>
<th>Recurrence</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>Tests</td>
<td>Patients</td>
<td>Tests</td>
<td>Patient</td>
</tr>
<tr>
<td>Never</td>
<td>38 (64)</td>
<td>174 (87)</td>
<td>178 (97)</td>
<td>1084 (99)</td>
<td>216 (89)</td>
</tr>
<tr>
<td>Ever</td>
<td>21 (36)</td>
<td>25 (13)</td>
<td>6 (3)</td>
<td>11 (1)</td>
<td>27 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>59 (100)</td>
<td>199 (100)</td>
<td>184 (100)</td>
<td>1095 (100)</td>
<td>243 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of recurrence</th>
<th>Ca 15-3 elevated (n)</th>
<th>Patient sensitivity (%)</th>
<th>Total number of recurrences (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any site</td>
<td>21</td>
<td>36</td>
<td>59</td>
</tr>
<tr>
<td>Liver-only</td>
<td>4</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Bone-only</td>
<td>7</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>Multiple sites</td>
<td>7</td>
<td>54</td>
<td>13</td>
</tr>
<tr>
<td>Lymph nodes-only</td>
<td>1</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Skin-only</td>
<td>1</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Lung-only</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Contralateral breast-only</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other site</td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>

CA 15-3: Uses and limitation as a biomarker for breast cancer

Michael J. Duffy a,*, Denis Evoy b, Enda W. McDermott b

Arguments for using marker

For some women, regular measurement of CA 15-3 provides the earliest evidence of recurrent/metastatic disease.

Three preliminary studies suggest that early treatment based on increasing marker levels improves outcome (63–65).

Intuitively, it might be expected that the earlier treatment is commenced, the better the outcome.

Availability of multiple forms of therapy for recurrent/metastatic disease.

Arguments against using marker

Lack of good (high-level) evidence that its measurement impacts on patient outcome or quality of life.

Low levels may provide false reassurance that patient is well.

Increasing marker levels in asymptomatic women causes stress and anxiety.

Marker is not elevated in all patients with recurrent/metastatic disease. (This lack of sensitivity might be minimised by measuring other markers such as CEA, TPA, TPS or HER2 extracellular domain).

Markers levels may increase due to certain benign diseases.

A clinically validated definition of marker increase is not available.

<table>
<thead>
<tr>
<th>Expert panel</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCO</td>
<td>No</td>
</tr>
<tr>
<td>ESMO</td>
<td>No</td>
</tr>
<tr>
<td>NCCN</td>
<td>No</td>
</tr>
<tr>
<td>EGTM</td>
<td>Yes</td>
</tr>
<tr>
<td>NACB</td>
<td>Not routinely but in certain situations</td>
</tr>
</tbody>
</table>
1846, stage I-II BC, ≥ 65 yrs

178 patients died due to breast cancer during 5 years of follow-up

Each additional surveillance mammogram was associated with a 0.69-fold decrease in the odds of breast cancer mortality (95% CI, 0.52 to 0.92)
“Careful history taking, physical examination, and regular mammography are recommended for appropriate detection of breast cancer recurrence”.

J Clin Oncol 2006,24:5091-5097
Cumulative incidence stages II to IV BC: 1.9% (95% CI, 0.2% to 3.7%) in the MRI-screened cohort vs 6.6% (95% CI, 3.8% to 9.3%) in the comparison group (P = .02).

Adjusted HR for the development of stages II to IV BC with MRI: 0.30 (95% CI, 0.12 to 0.72; P = .008).
CAUSES OF DEATH IN CANCER SURVIVORS  

1807 PTS

51% CANCER

49% OTHERS

FOLLOW-UP NOT ONLY CANCER RELATED

AACR, 2012
Survivors may be so focused on recurrence that they risk neglecting
- other aspects of their health
- long-term or late effects from treatment

As more time passes from the conclusion of active treatment, the risk for recurrence decreases and the need to focus on other aspects of survivor health should move to the forefront

Obesity, inactivity, poor dietary quality, and continued smoking linked to increased risk of cancer recurrence and mortality in individuals with common cancers

Heins M, J Clin Oncol 2012
Effect of Obesity on Prognosis After Early-Stage Breast Cancer

**Fig 1.** Cumulative incidence of first events (locoregional recurrences and distant metastases) in relation to body mass index (BMI) among 53,816 patients with early-stage breast cancer in Denmark, 1977 to 2006.

**Fig 2.** Risk of death as a result of breast cancer and other causes in relation to body mass index (BMI) among 53,816 patients with early-stage breast cancer in Denmark, 1977 to 2006.
The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial

DOI 10.1007/s10549-009-0512-0
LIFE STYLE

SURVEY ON
2,700 women with vs 20,700 women without cancer
• Higher rate of smoking
• Less likely to engage in exercise
• More likely to rate their health “as poor”

Am J Clin Oncol, 2012

Side effects/adverse events
• ↑ fatigue
• ↑ depression
• ↑ anxiety
• ↓ quality of life
• ↑ weight gain
• ↑ CVD risk
• ↑ cardiotoxicity
• ↑ bone loss/osteoporosis/fractures
• ↓ physical activity
“Fertility preservation is an issue of crucial importance in Adolescent and Young Adult (AYA) patients with cancer and should be an essential part in the management of their cancer. However, it is currently one of the most underprescribed and least implemented services in AYA patients with cancer.”

PF COCCIA J Natl Compr Canc Netw 2014
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

- Rates of major coronary events: 7.4% per gray, no apparent threshold
- Increase started within the first 5 years and continued into the 3rd decade after RT
- Proportional increase similar in women w/wo cardiac risk factors
One of the most life-threatening sequelae is a second malignant neoplasms (SMNs): 16% (or one in six) of cancers

Zhang Y, J Cancer Epidemiol 2012

Follow-up or screening for SMNs

Wood ME, J Clin Oncol 2012
Follow-up or screening for SMNs

Travis LB, J Natl Cancer Inst 2006
Concern about the preventive care provided to cancer survivors have two possible explanations:
  - for survivors and providers, the cancer diagnosis is the principal health care concern
  - uncertainty as to who is responsible for preventive care and for care during the follow-up

Grunfeld E, Can Fam Physician 2012
DEFINITION OF SURVIVORSHIP

- An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted.\(^a\)
- These guidelines focus on the vast and persistent impact both the diagnosis and treatment of cancer have on the adult survivor. This includes the potential impact on health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing.

STANDARDS FOR SURVIVORSHIP CARE\(^b\)

Care of the cancer survivor should include:
1. Prevention of new and recurrent cancers and other late effects
2. Surveillance for cancer spread, recurrence, or second cancers
3. Assessment of late psychosocial and physical effects
4. Intervention for consequences of cancer and treatment (e.g., medical problems, symptoms, psychologic distress, financial and social concerns)
5. Coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met.

\(^a\)Adapted with permission from the National Coalition for Cancer Survivorship as shown in the National Cancer Institute’s About Cancer Survivorship Research: Survivorship Definitions web page available at http://dccps.cancer.gov/ocs/definitions.html.

\(^b\)From Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council 2006. Available at: http://www.nap.edu/catalog/11468.html
American Society of Clinical Oncology Statement: Achieving High-Quality Cancer Survivorship Care
Mary S. McCabe, Smita Bhatia, Kevin C. Oeffinger, Gregory H. Reaman, Courtney Tyne, Dana S. Wollins, and Melissa M. Hudson

Quality of Life in Long-Term Breast Cancer Survivors
Tina Han, Marguerite Ennis, Nicky Hood, Margaret Graham, and Pamela J. Goodwin

Adherence to the World Cancer Research Fund/American Institute for Cancer Research Recommendations for Cancer Prevention Is Associated With Better Health-Related Quality of Life Among Elderly Female Cancer Survivors
Maki Inoue-Choi, DeAnn Lazovich, Anna E. Prizment, and Kim Robien

Provision and Discussion of Survivorship Care Plans Among Cancer Survivors: Results of a Nationally Representative Survey of Oncologists and Primary Care Physicians
Danielle Blanch-Hartigan, Laura P. Forsythe, Catherine M. Alfano, Tenbroeck Smith, Larissa Nekhlyudov, Patricia A. Ganz, and Julia H. Rowland
THE INCREASING INTEREST ON SURVIVORSHIP

Barriers to Breast and Colorectal Cancer Survivorship Care: Perceptions of Primary Care Physicians and Medical Oncologists in the United States
Katherine S. Virgo, Catherine C. Lerro, Carrie N. Klabunde, Craig Earle, and Patricia A. Ganz

American Society of Clinical Oncology Policy Statement: The Role of the Oncologist in Cancer Prevention and Risk Assessment
Robin T. Zen, Elizabeth Goss, Victor G. Vogel, Rowan T. Chlebowski, Ismail Jatoi, Mark E. Robson, Dana S. Wollins, Judy E. Garber, Powel Brown, and Barnett S. Kramer

Models for Delivering Survivorship Care
Kevin C. Oeffinger and Mary S. McCabe

ABSTRACT
Survivors of adult cancer face lifetime health risks that are dependent on their cancer, cancer treatment exposures, comorbid health conditions, genetic predispositions, and lifestyle behaviors. Content, intensity, and frequency of health care that addresses these risks vary from survivor to survivor. The aims of this article are to provide a rationale for survivor health care and to articulate a taxonomy of models of survivor care that is applicable to both community practices and academic institutions.

J Clin Oncol 24:5117-5124. © 2006 by American Society of Clinical Oncology
THE INCREASING INTEREST ON SURVIVORSHIP

Journal of Clinical Oncology Update on Progress in Cancer Survivorship Care and Research

Patricia A. Gerz, Fielding School of Public Health and David Geffen School of Medicine, University of California, Los Angeles; Jonsson Comprehensive Cancer Center, Los Angeles, CA
Craig C. Earle, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
Pamela J. Goodwin, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Cancer Survivorship Research and Guidelines: Maybe the Cart Should Be Beside the Horse

Craig C. Earle, Division of Population Sciences, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Published Ahead of Print on November 12, 2013 as 10.1200/JCO.2013.50.7442
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.7442


Jeffrey A. Meyerhardt, Pamela B. Marhu, Patrick J. Flynn, Larissa Korda, Charles L. Loprinzi, Bruce D. Mirsky, Nicholas J. Petrelli, Kim Ryan, Deborah H. Schrag, Sandra L. Wang, and Al B. Benson III
American Society of Clinical Oncology Statement: Achieving High-Quality Cancer Survivorship Care

Mary S. McCabe, Smita Bhatia, Kevin C. Oeffinger, Gregory H. Reaman, Courtney Tyne, Dana S. Wollins, and Melissa M. Hudson

Table 1. Components of Care to Consider When Developing Survivorship Care Plans

<table>
<thead>
<tr>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Account for the fact that some survivors may be at increased risk for other chronic diseases, such as diabetes and cardiovascular disease, and outline methods to address this risk.</td>
</tr>
<tr>
<td>Assess and address psychosocial needs</td>
</tr>
<tr>
<td>Include information about fertility planning for patients of reproductive age</td>
</tr>
<tr>
<td>Include known side effects (persistent and late occurring) of cancer and cancer treatment</td>
</tr>
<tr>
<td>Include screening guidelines and symptoms of cancer recurrence, including second primaries</td>
</tr>
<tr>
<td>Discuss and incorporate survivors' values and preferences regarding their care</td>
</tr>
<tr>
<td>Use discussions about cancer-related concerns as teachable moments to educate survivors about behavioral changes, such as tobacco cessation, obesity control, and alcohol usage reduction, regarding a variety of health issues</td>
</tr>
</tbody>
</table>
Breast cancer patients can be offered follow-up by their family physician without concern that important recurrence-related SCEs will occur more frequently or that the health-related quality of life will be negatively affected.

Grunfeld et al. J Clin Oncol 24:848-855
AWARENESS OF LATE EFFECTS OF CHEMOTHERAPY

- US survey of 1,130 oncologists and 1,072 PCPs
- LEs observed/seen reported for CTx to treat breast and colon cancers

<table>
<thead>
<tr>
<th>LEs</th>
<th>CTx agents</th>
<th>Oncologists (%)</th>
<th>PCPs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiotoxicity</td>
<td>Doxorubicin</td>
<td>95</td>
<td>55</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Paclitaxel</td>
<td>97</td>
<td>27</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Oxaliplatin</td>
<td>97</td>
<td>22</td>
</tr>
<tr>
<td>Menopause</td>
<td>CTX</td>
<td>71</td>
<td>15</td>
</tr>
<tr>
<td>SMNs</td>
<td>CTX</td>
<td>62</td>
<td>17</td>
</tr>
<tr>
<td>Main</td>
<td>All agents</td>
<td>65</td>
<td>6</td>
</tr>
</tbody>
</table>

- Oncologists must communicate this information to PCPs
- Education for all providers caring for cancer survivors is needed

Nekhlyudov L, JOP 2013
FOLLOW-UP: LOOKING BEYOND CANCER

- A periodic assessment is recommended for all survivors to determine any needs and necessary interventions.

- Health care providers encouraged to assess the following at regular intervals to determine whether reversible or contributing causes for symptoms exist:
  - (current disease status)
  - functional/performance status
  - medication
  - comorbidities
  - prior cancer treatment history and modalities used

*NCCN Guidelines V. 1.2014 Survivorship*
"the need for and value of participatory adaptation of each patient to risk-based programs tailored to address his or her specific risk and to promote general health

Surbone A, Ann Oncol 2013