



Factors that influence the quality of life of patients with colon and rectal cancer*

Fatores que influenciam a qualidade de vida de pacientes com câncer de cólon e reto

Factores que influyen en la calidad de vida de pacientes con cáncer de colon y recto

Adriana Cristina Nicolussi¹, Namie Okino Sawada²

ABSTRACT

Objective: To conduct an integrative literature review and evaluate the evidence regarding quality of life of patients with colon and rectal cancer. **Methods:** A literature search was conducted between 1997 and 2007 using the LILACS, CINAHL and MEDLINE databases. **Results:** The diagnosis and treatment of cancer affect several domains of quality of life of the sample of patients. A number of factors, such as, engaging in exercise, increased physical conditioning, good nutrition, and psychosocial support led to better quality of life. **Conclusions:** There was a lack of national publications, few publications by registered nurses, the predominance of descriptive studies, and weak level of evidence. We recommend that registered nurses conduct experimental studies to evaluate the effect of psychosocial interventions and physical activity programs in improving the quality of life of patients with cancer.

Keywords: Quality of life; Colorectal neoplasms; Oncologic nursing.

RESUMO

Objetivo: Foi realizada uma revisão integrativa da literatura com o objetivo de avaliar as evidências disponíveis na literatura o conhecimento científico produzido relacionado à qualidade de vida (QV) do paciente adulto com câncer de cólon e reto. **Métodos:** Selecionamos artigos publicados nas bases de dados LILACS, CINAHL e MEDLINE, entre 1997 e 2007. **Resultados:** Encontramos que o diagnóstico e o tratamento para o câncer afetam vários domínios da QV do paciente e que fatores como a prática de exercícios, aumento da aptidão física, o estado de boa nutrição, a presença de suporte psicossocial e de rede social favorecem uma QV melhor. **Conclusão:** Como lacunas no conhecimento, detectamos falta de produção científica nacional, escassa contribuição do enfermeiro, predomínio de estudos descritivos, de nível de evidência considerado fraco. Sugerimos a atuação do enfermeiro em pesquisas de intervenções de suporte psicossocial e de programas de atividade física que possibilitem melhorar a QV do paciente oncológico.

Descritores: Qualidade de vida; Neoplasias colorretais; Enfermagem oncológica.

RESUMEN

Objetivo: Fue realizada una revisión integradora de la literatura con el objetivo de evaluar las evidencias disponibles en la literatura el conocimiento científico producido relacionado a la calidad de vida (CV) del paciente adulto con cáncer de colon y recto. **Métodos:** Seleccionamos artículos publicados en las bases de datos LILACS, CINAHL y MEDLINE, entre 1997 y 2007. **Resultados:** Encontramos que el diagnóstico y el tratamiento para el cáncer afectan varios dominios de la CV del paciente y que factores como la práctica de ejercicios, aumento de la aptitud física, el estado de buena nutrición, la presencia de soporte psicossocial y de red social favorecen una CV mejor. **Conclusión:** Como vacíos en el conocimiento, detectamos: falta de producción científica nacional, escasa contribución del enfermero y predominio de estudios descriptivos con un nivel de evidencia considerado débil. Sugerimos la actuación del enfermero en investigaciones de intervenciones de soporte psicossocial y de programas de actividad física que possibilitem mejorar la CV del paciente oncológico.

Palabras clave: Calidad de vida; Neoplasia colorrectal; Enfermería oncológica.

* Study extracted from Master's Thesis presented to University of São Paulo at Ribeirão Preto College of Nursing, Ribeirão Preto (SP), Brazil.

¹ Graduate student (Ph.D.) at University of São Paulo at Ribeirão Preto College of Nursing, Ribeirão Preto (SP), Brazil.

² Associate Professor at General and Specialized Nursing Department, University of São Paulo at Ribeirão Preto College of Nursing, Ribeirão Preto (SP), Brazil.

INTRODUCTION

The evaluation of Quality of life (QoL) of cancer patients is an important indicator of patients' response to the disease and treatment.

This assessment considers the physical and psychosocial impact of diseases, dysfunctions or disabilities on patients, permitting a better knowledge of patients and their adaptation to the condition. In these cases, understanding about the patients' QoL is incorporated into health services' daily work, influencing health teams' decisions and therapeutic conducts⁽¹⁾.

This assessment makes it possible to understand how different interventions influence patient results⁽²⁾.

QoL assessment in cancer patients is important to provide information regarding treatment decisions, monitor disease symptoms and unwanted side effects and indicate interventions to improve QoL⁽³⁻⁴⁾.

Various items should be included in QoL assessment of cancer patients: physical, psychological and social wellbeing and their expectations for recovery, level of optimism and future life (5-6).

In the health area, the term health-related quality of life (HRQoL) has been used. It implies aspects more directly related to diseases or health interventions. Authors have used both QoL and HRQoL definitions, which can vary according to the study objectives and assessment instruments used.

HRQoL can be considered an optimal physical, mental/psychological, social, cognitive and functional level (role performance), including the assessment of patients' relationships, health perceptions, fitness, satisfaction with life, treatment and outcomes, wellbeing and future perspectives⁽⁵⁾.

As the physical, psychological, cognitive and social functions of patients with colon and rectal cancer are affected by the disease and treatment, the general aim of this research was to look for and assess evidence available in literature about scientific knowledge on QoL of adult patients with colon and rectal cancer.

The study objectives were: to characterize scientific production with regard to methodological characteristics and QoL aspects of adult patients with colon and rectal cancer, as well as to identify what instruments have been used for QoL assessment.

METHODS

The research method was an integrative literature review, which is considered a strategy to identify existing evidence to support a health practice in different specialties and is put forward as one of the instruments of Evidence-Based Practice⁽⁷⁻⁹⁾.

It is also considered a valuable part of the creation and organization process of literature, and should be marked by the same levels of clarity, rigor and replication as primary research⁽⁸⁾.

This method permits summarizing earlier research and reaching conclusions, considering the design of the assessed research, as well as synthesizing and analyzing existing scientific knowledge on the research theme⁽¹⁰⁾.

The question that guided this research was: "What scientific knowledge has already been produced on the quality of life of

adult patients with colon and rectal cancer?"

Three databases were used as sources for developing this research: LILACS, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Medical Literature Analysis and Retrieval System on-line (MEDLINE), with the following descriptors: "*qualidade de vida*" (quality of life), "*câncer colorretal*" (colorectal neoplasms) and "*enfermagem oncológica*" (oncologic nursing), including combinations between two or three descriptors in each database.

The following inclusion criteria were set to select the articles: articles with available abstracts about the QoL of adult patients with colon and rectal cancer; published between January 1997 and July 2007; in Portuguese, English and Spanish; indexed in LILACS, CINAHL and MEDLINE.

The exclusion criteria were: articles on methodological research, such as the creation and/or validation of QoL instruments and articles comparing treatment modes, such as the comparison between chemotherapy schemes, surgery types and treatment association, focusing on treatment efficacy assessment.

Publications were examined with the help of a research instrument⁽¹⁰⁾, which met the research objectives and permitted the studies' characterization by identifying the publication, quality of life assessment criteria and methodological characteristics, considering the articles' research design⁽¹¹⁻¹²⁾ and evidence level⁽¹³⁾.

RESULTS

The integrative review covered 24 articles. After a coherent analysis, the addressed themes were subdivided in six categories, which were: QoL and short-term survival (6 articles – 25%), QoL and long-term survival (3 articles – 12.5%), QoL and physical activity (3 articles – 12.5%), QoL and influence from follow-up exams (2 articles – 8.3%), QoL and psychosocial evaluation (6 articles – 25%) and QoL and aspects inherent to the patient (4 articles – 16.7%).

In this paper, the 15 articles in the following thematic categories will be discussed: QoL and physical activity, influence from follow-up exams, psychosocial evaluation and aspects inherent to the patient.

With regard to the main author, eight articles (53.3%) were published by physicians and one (6.6%) by a nurse, while authorship could not be identified in six (40%). According to the main authors' institution of origin, 10 (66.6%) articles are affiliated with universities, four (26.6%) with hospitals and one (6.6%) with the Danish Institute of Cancer Epidemiology.

As for the country that hosted the research, five (33.3%) articles were published in the United States, three (20%) in Germany and Canada, two (13.3%) in Denmark and one (6.6%) in Australia and Japan.

With regard to the journal, studies were found in 13 different journals, mostly medical, against two psychology and two cancer nursing journals.

When characterizing the studies in terms of QoL, it was found that a large majority, 12 (80%), did not use a QoL definition in the underlying research, and that only three articles (20%) contained a definition.

With respect to the instruments used, only the qualitative research did not use a QoL assessment instrument. The other articles used between one and five instruments in their research. Ten of these 14 articles justified why they chose the instruments that were used.

With regard to instrument validation, validated instruments were used in 11 articles. In the remainder, no reference was found to whether instruments had been validated for research. In total,

13 instruments were used in the assessed articles. The most used was the Quality of Life Questionnaire Core-30 (QLQ-C30) (six times), while other instruments were used between one and six times, as shown in Picture 1.

SF-12, SF-36, NHP and QLI are general instruments that assess the physical, emotional/mental, social and role function and general quality of life.

QLQ-C30 and FACT-G assess QoL in cancer cases, while

Picture 1. Quality of life instruments used in the review articles

INSTRUMENTS
Berkman-Syme Social Network Index (SNI) ⁽²⁰⁻²¹⁾
Centre for Epidemiological Studies Depression scale (CES-D) ⁽¹⁶⁾
EORTC Quality of Life Questionnaire Core-30 (QLQ-C30) ^(19,22,23,25-27)
EORTC Quality of Life Questionnaire Colorectal-38 (QLQ-CR38) ^(19,23,25-26)
Functional Assessment of Cancer Therapy - Colorectal (FACT-C) ⁽¹⁴⁻¹⁶⁾
Functional Assessment of Cancer Therapy - General (FACT-G) ⁽¹⁶⁾
Hospital Anxiety and Depression Scale (HADS) ^(18,22-23)
Medical Outcomes Study Short-Form 12 (SF-12) ^(18,21)
Medical Outcomes Study Short-Form 36 (SF-36) ⁽²⁰⁾
Nottingham Health Profile (NHP) ⁽¹⁷⁾
State-Trait Anxiety Inventory (STAI) ⁽¹⁶⁾
Satisfaction With Life Scale (SWLS) ⁽¹⁴⁻¹⁶⁾
The Ferrans and Powers Quality of life Index (QLI) ⁽²⁸⁾

Obs. Notes refer to the articles that used each instrument.

Picture 2. Knowledge synthesis according to thematic categories: QoL and Physical Activity and QoL and Influence from Follow-up Exams.

Thematic category	Studies	Design/evidence level	Affected QoL domains	Knowledge synthesis
QoL and Physical Activity	<p>Courneya e Friedenreich 1997⁽¹⁴⁾ Courney a et al. 1999⁽¹⁵⁾ Courney a et al. 2003⁽¹⁶⁾</p> <p>Assessed patients' QoL and physical activity and correlated these data to investigate whether physical activity level interferes in patients' QoL</p>	<p>Descriptive and exploratory research – level 6⁽¹⁴⁾</p> <p>Cohort study – level 4⁽¹⁵⁾</p> <p>Controlled randomized clinical trial – level 2⁽¹⁶⁾</p>	<p>Role function and specifics of colorectal cancer</p>	<p>Cancer treatment negatively affects exercise levels. Physical activity and increased cardiovascular fitness are associated with improved QoL and can decrease anxiety in survivors of colorectal cancer.</p>
QoL and Influence from Follow-up Exams	<p>Kjeldsen et al. 1999⁽¹⁷⁾ Wattchow et al. 2006⁽¹⁸⁾</p> <p>Followed patients through exams⁽¹⁷⁾ and different follow-up types⁽¹⁸⁾ and their influence on QoL.</p>	<p>Prospective cohort study – level 4⁽¹⁷⁾</p> <p>Controlled randomized clinical trial – level 2⁽¹⁸⁾</p>	<p>Physical function at baseline and which improved during the research.</p>	<p>The group that received more intense follow-up reported a better HRQoL with a small but statistically significant difference.</p> <p>No significant differences were found for type of follow-up according to the clinician or surgeon.</p>

Picture 3. Knowledge synthesis according to thematic categories QoL and Psychosocial Evaluation and QoL and Aspects Inherent to the patient.

Thematic category	Studies	Design/evidence level	Affected QoL domains	Knowledge synthesis
QoL and Psychosocial Evaluation	Kerr et al. 2003 ⁽¹⁹⁾ Sapp et al. 2003 ⁽²⁰⁾ Sultan et al. 2004 ⁽²¹⁾ Tsunoda et al. 2005 ⁽²²⁾ Ross et al. 2005 ⁽²³⁾ Houldin and Lewis 2006 ⁽²⁴⁾ Assessed QoL and its relation with psychosocial aspects, such as anxiety and depression and aspects related to social support offered, including the social network and instrumental, emotional and informational support.	Descriptive and exploratory studies – level 6 ⁽¹⁹⁻²²⁾ Controlled randomized clinical trial – level 2 ⁽²³⁾ Qualitative, phenomenological – level 6 ⁽²⁴⁾	Role, emotional, social, physical and mental functions. Patients presented a deficit for body images and symptoms like depression, anxiety and insomnia; and reported financial problems.	Concluded that patients need social support. Factors such age, gender, body mass increase, presence of comorbidities, anxiety and depression influenced HRQoL. The psychosocial intervention led to an improvement in the social function and in short-term fatigue.
QoL and Aspects Inherent to the patient	Schmidt et al. 2005 ⁽²⁵⁾ Schmidt et al. 2005 ⁽²⁶⁾ Gupta et al. 2006 ⁽²⁷⁾ Lis et al. 2006 ⁽²⁸⁾ Studies tested the correlation among genders ⁽²⁵⁾ , age ranges ⁽²⁶⁾ , described the difference between well- and malnourished patients ⁽²⁷⁾ and investigated whether QoL predicts survival ⁽²⁸⁾ .	Cohort studies – level 4 ^(25,26) Descriptive and exploratory studies ⁽²⁷⁻²⁸⁾	Physical function and global QoL Fatigue, nausea and vomiting, insomnia, constipation and diarrhea symptoms in women and impaired sexual satisfaction in men. Physical function, fatigue and pain in patients > 70 years. Role function, global QoL, fatigue and insomnia in undernourished patients.	The results indicate that female gender, age over 70 years and malnutrition are associated with worse QoL. Physical function, global QoL, treatment history and tumor staging at the time of diagnosis were significantly associated with survival.

QLQ-CR38 and FACT-C are specific for colorectal cancer; these instruments include items to assess the following symptoms: pain, insomnia, fatigue, nausea and vomiting, appetite loss and questions about intestinal, urinary and sexual functioning and body image.

The remaining instruments assess specific issues: the HADS, CES-D and STAI look at anxiety and depression, SNI at the social network and SWLS assesses satisfaction with life.

Pictures 2 and 3 show a knowledge synthesis according to the

studies' theme categories, research design and evidence level.

DISCUSSION

Quality of life research in patients with colorectal cancer has considerably evolved in the last five years, as a result of the development of two specific instruments: QLQ-CR38 and FACT-C. Many studies have used a range of different instruments in addition to these⁽²⁹⁾, as revealed in this review, where 12 (80%)

articles were published after 2003, besides the diversity of instruments identified.

Colorectal cancer treatment may negatively affect HRQoL. However, despite rapid treatment advances, QoL and associated health results generally are not measured. One of the potential barriers to adopt this practice is the confusion caused by the range of QoL assessment instruments. Moreover, physicians frequently do not know how to interpret HRQoL data and may not consider HRQoL measures as an additional contribution to choose treatment or make decisions⁽²⁹⁾.

Nurses' low contribution level as the main author (only one article), two articles published in nursing journals and no contribution in Brazilian journals were also observed. Contemporary nursing needs to face some challenges. The nursing education process needs modernization, students need to be encouraged to participate in research and community service activities and included in academic research groups; researchers should submit their papers to peer-reviewed journals and journal editors should make efforts to improve editorial quality and indexation in Brazilian and international databases⁽³⁰⁾.

As for QoL assessment aspects, the present results show flaws in the use of the QoL concept, as identified in a study⁽³¹⁾ that detected that only 11 (15%) out of 75 articles reviewed defined the term; 14 years after that publication, this gap/deficiency in research continues, as only three out of 15 articles analyzed here use a concept for the term. It is important for authors to use a definition of QoL in their research and express what aspects they will investigate.

Despite this deficiency, studies improved with regard to the instruments used, with 10 articles justifying their choices and 11 using validated instruments, as the use of validated instruments is important for reliable results.

An analysis of methodological characteristics showed 14 (93.3%) quantitative and only one (6.6%) qualitative research paper.

With respect to the research design and evidence level, the

qualitative article – a phenomenological study, together with the seven (46.6%) descriptive studies, are classified as evidence level 6, which is considered weak. Four (26.6%) level 4 (cohort) and only three (20%) level 2 articles were found, considered strong, i.e. randomized clinical trials, with an experimental design.

Progress has been made in cancer research, including treatment, prevention, survival and QoL; most of this research, however, is done in the medical area, funded by colleges, with little nursing participation, which remains limited to non-experimental research⁽³²⁾.

CONCLUSIONS

Cancer diagnosis and treatment affect different HRQoL domains of colon and rectal cancer patients. Factors like physical exercise, increased cardiovascular fitness, well-nutritional condition and the presence of psychosocial support and a social network benefit a better QoL.

Knowledge gaps, however, were revealed by the lack of research with strong evidence, that is, intervention studies, as most research is descriptive; the lack of Brazilian scientific production on the theme and nurses' lack of participation as principal investigators.

Quality of Life is an emerging term and research on the theme has been developed in theses and dissertations at Brazilian colleges. It is difficult though, to find publications resulting from these studies in journals indexed in databases. In order to improve the Brazilian scientific production scenario, interaction is needed between clinical nurses, researchers and educators⁽¹⁰⁾.

Nurses can be active in QoL assessment studies of colon and rectal cancer patients through psychosocial support interventions for individuals and their families, including emotional, informational and instrumental support; through physical exercise programs and relaxation sessions, provided that there are no contraindications, leading to physical, mental and social wellbeing and, consequently, to a better HRQoL.

REFERENCES

- Morris J, Perez D, McNoe B. The use of quality of life data in clinical practice. *Qual Life Res.* 1998;7(1):85-91.
- Koop I, Bauhofer A, Koller M. Understanding quality of life in patients with colorectal cancer: comparison of data from a randomised controlled trial, a population based cohort study and the norm reference population. *Inflamm Res.* 2004;53 Suppl 2:S130-5.
- Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Hölzel D. Comparison of breast and rectal cancer patients' quality of life: results of a four year prospective field study. *Eur J Cancer Care (Engl).* 2003;12(3):215-23.
- Sawada NO. Qualidade de vida dos pacientes com câncer de cabeça e pescoço [tese]. Ribeirão Preto: Escola de Enfermagem de Ribeirão Preto da Universidade de São Paulo; 2002.
- Bowling A. Measuring disease: a review of disease-specific quality of life measurement scales. 2nd ed. Buckingham; Philadelphia: Open University Press; c2001.
- Santos SR, Santos IBC, Fernandes MGM, Henriques MERM. Qualidade de vida do idoso na comunidade: aplicação da escala de Flanagan. *Rev Latinoam Enferm.* 2002;10(6):757-64.
- Beyea S, Nicoll LH. Writing and integrative review. *AORN J.* 1998;67(4):877-80.
- Ganong LH. Integrative reviews of nursing research. *Res Nurs Health.* 1987;10(1):1-11.
- Poletti NAA. O cuidado de enfermagem a pacientes com feridas crônicas: a busca de evidências para a prática [dissertação]. Ribeirão Preto: Escola de Enfermagem de Ribeirão Preto, Universidade de São Paulo; 2000.
- Nicolussi AC. Qualidade de vida de pacientes com câncer de cólon e reto: revisão integrativa da literatura [dissertação]. Ribeirão Preto: Escola de Enfermagem de Ribeirão Preto da Universidade de São Paulo; 2008.
- Polít DF, Beck CT, Hungler BP. Fundamentos de pesquisa em enfermagem. 5a. ed. Porto Alegre: Artmed; 2004.

12. Lobiondo-Wood G, Haber J. Nursing research: methods and critical appraisal for evidence-based practice. 6th ed. St. Louis: Mosby/ Elsevier, 2006.
13. Melnyk BM, Fineout-Overholt E. Making the case for evidence-based practice. In: Melnyk BM, Fineout-Overholt E. Evidence-based practice in nursing & healthcare: a guide to best practice. Philadelphia: Lippincott Williams & Wilkins; 2005. cap1, p. 3-24.
14. Courneya KS, Friedenreich CM. Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. *J Altern Complement Med.* 1997;3(3):215-26.
15. Courneya KS, Friedenreich CM, Arthur K, Bobick TM. Physical exercise and quality of life in postsurgical colorectal cancer patients. *Psychol Health Med.* 1999;4(2):181-7.
16. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, Farey AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care (Engl).* 2003;12(4):347-57.
17. Kjeldsen BJ, Thorsen H, Whalley D, Kronborg O. Influence of follow-up on health-related quality of life after radical surgery for colorectal cancer. *Scand J Gastroenterol.* 1999;34(5):509-15.
18. Wattoo DA, Weller DP, Esterman A, Pilotto LS, McGorm K, Hammett Z, et al. General practice vs surgical-based follow-up for patients with colon cancer: randomised controlled trial. *Br J Cancer.* 2006;94(8):1116-21.
19. Kerr J, Engel J, Shlesinger-Raab A, Sauer H, Hölzel D. Doctor-patient communication: results of a four-year prospective study in rectal cancer patients. *Dis Colon Rectum.* 2003;46(8):1038-46.
20. Sapp AL, Trentham-Dietz A, Newcomb PA, Hampton JM, Moynihan CM, Remington PL. Social networks and quality of life among female long-term colorectal cancer survivors. *Cancer.* 2003;98(8):1749-58.
21. Sultan S, Fisher DA, Voils CI, Kinney AY, Sandler RS, Provenzale D. Impact of functional support on health-related quality of life in patients with colorectal cancer. *Cancer.* 2004;101(12):2737-43.
22. Tsunoda A, Nakao K, Hiratsuka K, Yasuda N, Shibusawa M, Kusano M. Anxiety, depression and quality of life in colorectal cancer patients. *Int J Clin Oncol.* 2005;10(6):411-7.
23. Ross L, Thomsen BL, Karlsen RV, Boesen EH, Johansen C. A randomized psychosocial intervention study on the effect of home visits on the well-being of Danish colorectal cancer patients – The INCA Project. *Psychooncology.* 2005;14(11):949-61.
24. Houldin AD, Lewis FM. Salvaging their normal lives: a qualitative study of patients with recently diagnosed advanced colorectal cancer. *Oncol Nurs Forum.* 2006;33(4):719-25.
25. Schmidt CE, Bestmann B, Kuchler T, Longo WE, Rohde V, Kremer B. Gender differences in quality of life of patients with rectal cancer. A five-year prospective study. *World J Surg.* 2005;29(12):1630-41.
26. Schmidt CE, Bestmann B, Kuchler T, Longo WE, Kremer B. Impact of age on quality of life in patients with rectal cancer. *World J Surg.* 2005;29(2):190-7.
27. Gupta D, Lis CG, Granick J, Grutsch JF, Vashi PG, Lammersfeld CA. Malnutrition was associated with poor quality of life in colorectal cancer: a retrospective analysis. *J Clin Epidemiol.* 2006;59(7):704-9.
28. Lis CG, Gupta D, Granick J, Grutch JF. Can patient satisfaction with quality of life predict survival in advanced colorectal cancer? *Support Care Cancer.* 2006;14(11):1104-10.
29. Wilson TR, Alexander D, Kind P. Measurement of health-related quality of life in the early follow-up of colon and rectal cancer. *Dis Colon Rectum.* 2006;49(11):1692-702.
30. Marziale MHP. Produção científica da enfermagem brasileira: a busca pelo impacto internacional. *Rev Latinoam Enferm.* 2005;13(3):285-90.
31. Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. *JAMA.* 1994;272(8):619-26.
32. Ozols RF, Herbst RS, Colson YL, Gralow J, Bonner J, Curran WJ Jr, et al. American Society of Clinical Oncology. Clinical cancer advances 2006: major research advances in cancer treatment, prevention, and screening - a report from the American Society of Clinical Oncology. *J Clin Oncol.* 2007;25(1):146-62.