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Economic evaluation of chemotherapy

Cost, quality of life and outcome measures in ovarian cancer

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As research into cancer intensifies and treatments proliferate, life-interval gained is no longer a question of simply measuring time. Ovarian cancer patients, especially, have benefited from efforts to develop feasible screening processes and the new treatment modalities for this type of cancer. Within the last decade, medicine has come to realize that survival intervals and cure rates are useless to patients if they cannot retrieve out of the process at least some aspects of their lives before cancer and for as long a period of time as possible. This article focuses on measuring and assessing the effects of treatment in terms of outcome and quality of life from the patient's perspective. Medicine as a science, and being a science, has not been comfortable in taking into account intangibles when assessing its own performance and success rates. However, the roles of caregivers and health providers have been rapidly evolving from that of treating the disease to treating the patient, and often the patient's family, with all that implies. [© 1998 Lippincott Williams & Wilkins.]

Key words: Assessment, cost, measure, outcome, ovarian cancer, quality of life.

Introduction

Ovarian cancer is not usually thought of as a disease that can be cured by clinicians, but over the last two decades subgroups of patients have been better defined for a clearer understanding of the cure rate for these patients. Since cure is elusive and the overall survival rate seems to have plateaued,[1] other ways to measure success must be used. Because most advanced stage patients do not survive their disease, the cost of various treatments as well as the patients' quality of life and the outcome measures of different therapies have come into larger play over the past several years. Ovarian cancer affects women throughout their age groups, but predominantly in later life. Germ cell tumors usually affect women less than age 30; epithelial ovarian cancers affect women in their prime productive years between the ages of 40 and 70. Approximately 20 000 new cases of ovarian cancer are diagnosed every year in the US. It accounts for approximately 12 000 deaths and is the fourth leading cause of death from cancer.[2] The response of ovarian cancer to treatment is substantially high; however, the epithelial variety tends to recur with resistant cell clone lines to which the patient ultimately succumbs. The tumor is inherently sensitive to chemotherapy, hence there is a plethora of drugs that are initially active in this disease, probably more so than with any other solid tumor. Therefore, options and preferences are dependent on the circumstances of the patient.

When dealing with ovarian cancers, the hallmark is pathological tissue demonstrating the malignancy. Before discussing cost, quality of life and outcome measures in ovarian cancer, a brief history of chemotherapy in ovarian cancer, as well as treatment, is in order. Once the diagnosis of ovarian cancer is made, multimodality of treatment is necessary. The primary treatment of ovarian cancer requires surgical removal of the tumor. When followed by chemotherapy the response rate affords the patient a long disease-free interval. However, the treatment of ovarian cancer has been rather frustrating because, though many drugs seem to produce an initial response, the ultimate survival of the patient has not changed much overall during the last two decades.[3]

History

In the 1970s the research in epithelial cancer was boosted by Griffith's study showing that cytoreductive surgery improves survival in patients.[4] The chemother-

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apeutic drugs used at that time included thiotepa, melphalan and 5-fluorouracil. The introduction of cisplatin in the late 1970s was another demonstrable advantage for patients with ovarian cancer.[5] Different forms of toxicity were encountered and strategies were used to overcome them.[6,7] These strategies, including the administration of colony stimulating factor and erythropoetin, enable clinicians to continue administration of the same dose of chemotherapy rather than decreasing it. However, this comes at a cost.[8,9] This is important to remember, since in all retrospective analyses it is difficult to predict cost of future treatment. As new agents are introduced which decrease toxicity,[10] the overall cost in the treatment of this malignancy will continue to increase. Measures for quality of life and other measures of outcome as a final endpoint become more important. In the 1990s, the introduction of taxol showed a clear survival advantage in patients with ovarian cancer.[11] Thus, an analysis of cost-effectiveness in ovarian cancer is usually measured by dollars per life-year saved as used to measure similar outcomes by other authors.[12]

On the other hand, germ cell tumors of the ovary are difficult to measure in such ways because these offer better success stories of patient cures. In the past, the diagnosis of germ cell tumor was uniformly fatal. It is now far less common for these to resist cure. The age at diagnosis is usually young, ranging from age 7 to 45. It is associated with pregnancy and the usual symptoms include a rapidly enlarging pelvic mass with abdominal pain. Tumor markers, including alfa fetal protein, lactic dehydrogenase and human chorianic gonadotropin, are elevated. Most patients undergo surgery and chemotherapy. Successful treatment measures for these tumors include belomycin, etoposide and cisplatin.[13] With these drugs come the potential for pulmonary toxicity; however, omitting bleomycin does decrease the overall survival.[14] Therefore, quality of life with treatment of germ cell tumors may be viewed as decreasing in order to increase overall survival; patients with ovarian cancer are willing to accept more toxicity for cure.[15] Because over 90% of patients can be cured of germ cell tumors with this chemotherapeutic regimen, cost-effectiveness is difficult to calculate as life-year saved, but rather can be calculated as equally effective regimens that cost less.

Measuring tangibles and intangibles

Quality of life is important and integral to a discussion of cost-effective treatments. Outcome measurement attempts to define a more appropriate method. The data on cost-effectiveness in ovarian cancer is rather scant and is covered in more detail in another part of this special issue with chemotherapy and taxenes for ovarian cancer. Quality of life is very personal and mostly assessed through subjective means in which patients are given follow-up questionnaires. This makes reliability lower for methods of measurement. There has been concern that the restructuring of health care with its emphasis on more cost-cutting measures will motivate the medical health care establishment to deliver less quality of care and this will indirectly cause a decrease in overall quality of life in patients, even though the cost may be lessened.[16] There has been more of a trend recently for insurance companies and Health Maintenance Organizations to steer patients away from speciality oncology care. In the US, limitation on selection of treatment options has put a lot of pressure on physicians who continue to deliver high quality care.[17] In treatment for ovarian cancer it would be very easy if more patients were cured, thereby making the cost more favorable since more life would be bought for the cost of treatment per patient. However, because the overall cure rates for epithelial cancer are not high, restoring the patient back to her usual social and home environment with a good sense of well-being and self-esteem becomes more imperative. This can be done in the curative as well as the palliative setting.[18]

Screening

The methods for screening have not been easily formulated. Consequently, cost-effectiveness for screening for ovarian cancer has not been studied. Preferably, screening would be performed with a low cost tool that has easy follow up. Because laparotomy is required for diagnosis in ovarian cancer, the ideal screening tool has been elusive. The costs and effects of screening for other gynecological malignancies, including cervical and breast cancer, even in an Emergency Room setting, have been worked out.[19] Overall, screening for cervical and breast cancer is cost effective; however, in ovarian cancer this is not the case. The prevalence and intervention in ovarian cancer are different from the others. Serum CA125 measurement as well as vaginal ultrasound have been attempted as screening modalities for ovarian cancer but cost-effectiveness as well as impact have not been well established. Most ovarian cancers are not found on routine examination as they usually present with symptoms.[20] It has been estimated that 10 000

bimanual examinations will need to be performed for one asymptomatic ovarian carcinoma to be found.[21] When CA125 is used as a screening tool the predictive value, though it has high sensitivity and specificity, is only 1.72% in the screening population.[22] The use of vaginal ultrasound improves the predictive value to 42.3%.[23] In high-risk patients with a strong family history of ovarian cancer it may be worthwhile to combine vaginal ultrasound and CA125 procedures. The strong family history element attempts to pool a subpopulation of patients with increasing prevalence, hence prevalence directly impacts on predictive value. The cost-benefit ratio is incorporated into this. However, in the general population where the prevalence of ovarian cancer is low, it is difficult to justify routine ovarian cancer screening with the methods presently available.[24] In screening populations, the estimated cost of an ultrasound and CA125 as screening tools for ovarian cancer are thought to increase the cost of health care by $14 billion.[25]

In using CA125, sensitivity and specificity are important but can also be compared to other modalities that are used in mass screening. Prostate cancer screening of all men over the age of 50 has been pushed by the mass media, as well as some famous celebrities. With over 30 million men over the age of 50 in the US and the use of a PSA test costing approximately $37.00 per test and $50.00 for a digital rectal exam, approximately $2.5 billion would be added to the annual health care budget.[26] This is combined with the fact that the PSA has a sensitivity of 62.8% and a specificity of 89.6%.[27] This is lower than is usual for a CA125. Even when compared with mammography as initial screening tools, the sensitivity for mammography is 92% and the specificity is 94.9%.[28] That has a positive predictive value of only 10%, the difference being the prevalence of prostate cancer as well as breast cancer. However, it does cast a different light on CA125 screening in looking at these different positive predictive values.

Cost

The cost of life per year gained is important in the assessment of primary ovarian cancer and chemotherapy. In a salvage setting, the emphasis shifts and the response rate would be life gained as an assessment value. Salvage agents in epithelial ovarian cancer include gemcitabine, novalbine, doxcil and hexalin, as well as other agents. Though these agents have a response rate, the actual overall survival has not been shown to be improved and, therefore, a cost-effectiveness analysis is more difficult. Gemcitabine has been shown to be cost-effective in non-small cell lung cancer because it improved overall survival.[29] To be cost-effective, a chemotherapeutic agent should add more life for patients or impact quality of life in a measurable way. How to measure this in a precise way will be discussed later in this article. Taxol and cisplatin have been shown to be cost-effective in advanced ovarian cancer.[30,31] The kinetics of CA125 dropping after initial chemotherapy were also analyzed to show a potential cost-effective way to continue or change chemotherapy in ovarian cancer patients.[32] Patients whose drop in CA125 slows would not benefit from the present chemotherapy. This would save funds if courses of chemotherapy not essentially effective were eliminated.

Cost-effectiveness analysis is not something than can be viewed in a vacuum. Population perspective and point of view play a pivotal role in what is ultimately done. Ubel brought this to light in an interesting study.[33] In this study those surveyed, including jurors, experts in medical policy and medical ethicists, were asked whether they would accept a test that would screen a smaller population but was more cost-effective. It would screen only half the population and save 1100 lives versus a less effective test that would screen the entire population and save 1000 lives. The ethical concerns raised and expressed by the majority of those surveyed was that limiting the test to half the population, though more cost-effective, was unethical. Even in people who analyze medical policy in a medical decision modality did not want limits on the test. The importance of this study shows that public perception must be assessed in trying to come up with a screening test that is more cost-effective. If a test is perceived to be cost-effective but access to it is not uniformly given to patients, the test is perceived as unethical. This must be factored into cost-effective analysis and overall health care policies. The attributable costs for a specific disease, such as ovarian cancer, are difficult to define. In trying to measure the direct and indirect costs of ovarian cancer, there is very little data to go on in showing these costs. Etzioni estimated that the average present value of 15 year costs attributable to ovarian cancer was slightly over $21 000 for local disease and $32 000 for distant disease in 1991 US$.[34] The data was limited to Medicare claims and therefore had an older population. They were able to link the Medicare claims data with the Surveillance, Epidemiology and End Results (SEER) cancer registry database.

The difficulty in teasing out the direct cost of ovarian cancer is also related to use of the Intensive Care Unit (ICU) and overall survival. The long and

radical surgeries performed on ovarian cancer patients lead the patients to be admitted to the ICU for several days after the surgery, therefore looking at the costs of the ICU setting is salient. Recurrent ovarian cancer patients who undergo surgery requiring a prolonged stay in the ICU have a 41% death rate in the hospital and a median survival of 50 days.[35] The findings of this study showed that cardiac disease and surgical ICU stays of greater than 5 days were factors in poor prognoses. When costs were looked at in the study, oncology patients cost more during each hospitalization; however, the ratio of SICU cost to total hospitalization cost was lower in oncology patients because they usually had, overall, a larger total of hospital days. These oncology patients were compared to OB/GYN patients who did not have gynecological malignancies.[36] The ovarian cancer patients had a median cost of $29 780 per total hospital stay. Median cost per day gained was $595. The ovarian cancer patients that ultimately died of their disease or had no evidence of disease at the end of follow-up did not have a difference in the mean cost per patient hospital stay. Age did not have much of an impact in hospital cost with equal costs over the same age distribution.

Measurement of the quality of life

This portion of the article will discuss measurement of the quality of life. This measurement tries to quantify the overall functional aspect of the patient, not necessarily toxicities of chemotherapy but overall social well-being and comfort. It also focuses this measurement on the patient's point of view.[37,38] Translation of this is a rather complex task and draws from many fields of the social sciences.[39] It would be simple to ask patients to measure their quality of life. Various rating scales can be objectified. However, each measuring tool has a balance between subjective and objective components.[40] The basic elements of constructing a measure or scale for quality of life directs that items be measured and given a value scale.[41] This value scale can then be summed and a score given. These scores can be combined and a computer-generated, statistically normal distribution can be obtained.[42] Within this value, though, the items that are covered should include both objective and subjective components. In essence, not only are such important variables covered, such as reduction in size of tumors on CAT scan, or a decreasing CA125, but overall the patient's ability to function at home, decrease her Emergency Room visits and decrease episodes of sepsis. These values need to be reliable and consistent depending on the conditions being measured against. Repeated measures with the same test under the same conditions should give similar results. Validity should also be inherent in this value in that it purports to measure exactly what it is trying to do. The scale should also be responsive in that a decrease in it should reflect a decrease in the overall quality of life.[43] Changes should also be such that a change in the quality of life in various degrees should be appropriate in the amount such that small changes are reflected by a value that is measured and large changes also reflect large changes in quality of life.

In oncology,[44,45] many methods have been validated in measuring quality of life as well as other illnesses.[46,47] Defining quality of life has been elusive with many definitions given.[48,49] Difficulty in definition need not mean that certain weight cannot be assigned in order to compare it and determine the presence of improvement. In measuring quality of life, various approaches can be used including the Sickness Impact Profile,[50] which measures general health parameters, or the Functional Living Index in Cancer,[45] identifying the more specific disease impact on a patient's condition. Incorporating cost-effectiveness in quality of life measurements includes cost-utility approaches.[51] These are much more appropriate for health policy and global approaches if these are to ultimately be of any value. The modified approach of this was developed to discover quality of life as impacted by chemotherapy for early-stage breast cancer.[52] This quality-of-life measure is called the quality-adjusted-time without symptoms and toxicity (Q-TWiST). This measure is used for several processes and gives a more detailed perspective of the patient; however, the weights towards how important the patient's problems are remain less obvious. The Q-TWiST approach tries to separate the different kinds of treatments that the patient is receiving, and it infers patient preferences and impact on quality of life. Other measures of quality of life include the Medical Outcome Study from which is derived the Short-Form-36.[46,47] Though this self-reporting measure is very reliable with patients that are quite ill, it may not be accurate. In essence, patients may be too sick to fill out the forms or too ill to state exactly how they are feeling. When family members or surrogates are used, at times reliability can be disappointing.[53] This differs from what others have reported.

In thinking of how to measure quality of life, two variables need to be considered separately; reliability and validity. Reliability simply means how repeatable a certain measure may be, though it may not be very accurate by virtue of the different populations involved. Correlations between different measures of

quality of life become important. Therefore, the above-mentioned examples of measuring quality of life have relatively high reliability with correlation coefficients of about 70%.[54] Reliability is not a fixed entity and does have some variations because of the subjective nature of the questions applied to quality of life issues. Reliability depends on a number of items. The more questions and variables that are measured, the higher the reliability. However, there has to be a balance without overburdening the patient and the health care staff in trying to obtain that information; then the test and measure become useless because there are too many coefficients. Validity, on the other hand, reports on how accurately what is being measured truly reflects the natural phenomenon. Therefore, errors can be made by applying some measures of quality of life when they do not truly reflect these natural phenomena. Overall validity results when the health quality measure measures illness as well as overall well-being. Other measures include the Quality-of-Life Index (QLINR) with its five areas of functioning on a 10-point scale. This measure has been useful in comparing patients with terminal illness versus patients undergoing active treatment. Its reliability is slightly low, being 0.6.[55] A slight modification of this includes the Ferrans and Powers Index. This format is a two-part response which rates satisfaction and perceived importance in quality of life areas.[56] There is a cancer-specific form of this with reliability of 0.65–0.93. More recently, the Society of Gynecological Oncologists has been interested in outcomes; Quality of Life Measure with the Medical Outcomes Study—Short-Form Health Status Survey.[46] This form is made slightly shorter to 26 questions and is now being used by the Society of Gynecological Oncologists to measure quality of life as well as outcomes in specific disease-related entities. Complementary care has also been introduced into mainstream gynecological oncology as presented by Granai *et al.* at the last gynecological oncology meeting.[57] He demonstrated that the use of scientific methods, quality of care and perceived complementary care can be beneficial to patients. Short-Form-36 has high reliability, ranging between 0.73 and 0.94. It can distinguish between patients with chronic conditions and determine the severity of illnesses.[47]

Quality of life

The role of nursing has been pivotal in spearheading a lot of the research into quality of life. Quality of life includes subtle issues such as fatigue, depression and anxiety, and the realities and differing values of the elderly. In quality of life assessment, fatigue can be improved by simple intervention.[58] Maximizing nutritional parameters helps with this as it can minimize therapeutic side effects.[59] There is a high rate of depression and anxiety in families dealing with ovarian cancer. Identifying depression and anxiety in patients can lead to early intervention and circumvent some long-term sequelae.[60] The values and preferences of the individual patient as well as the amount of input the patient desires to contribute can be assessed.[61] In elderly patients with ovarian cancer, life expectancy and co-morbidity have to also be taken into account.[62] The elderly may have different objectives and points of view which need to be taken into consideration. This quality of life assessment is useful and can be performed by the caregivers as well as the patient's physicians to determine the optimal quality of life for that patient.[63] For long-term survivors of female cancers many of the physical concerns may be resolved, but not the spiritual and philosophical issues. A multi-purpose support team was recommended to carry on to improve this quality of life.[64] Since many ovarian cancer patients ultimately succumb to their disease, the quality of life in patients receiving hospice care should be considered. It is important to realize that even at this stage of care, intervention is possible and quality of life for hospice patients can be improved.[68] More recently, autologous stem cell transplantation has been used as an aspect of ovarian cancer treatment. It has gone from being regarded as salvage therapy to up-front consideration. The quality of life issue most affected in patients undergoing stem cell transplantation was physical health, though the overall emotional status was poor throughout the stem cell transplant procedure.[65] Intervention to improve quality of care has included exercise as well as other supportive measures.[66] In measuring quality of life it is important to use a standard measurement where results can be compared.[67]

Overall well-being is the absence of physical disease as well as overall social well-being.[68] Research in quality of life issues as well as outcome has grown in the last decade as more evaluations of the efficacy of cost-effective techniques are being scrutinized.[69] Quality of life issues affect physical, social and psychological arenas, and are influenced by the person's perceptions, expectations and beliefs.[70,71] The subjective and objective measurements are intimately interwoven so as to come to a perceived measure of quality.[72,73] Because there are an infinite number of health components, each formulated assessment measure has to be used according to the situation being assessed.

Overall, there are approximately 49 000 women who have become long-term survivors of gynecological cancers each year in the US.[74] From the beginning, age of diagnosis will have an impact on the quality of life as clearly, if they are young, fertility will be at issue.[75] Luckily, germ cell tumors can usually be treated in reprodutive conservative fashions. In the family setting, once the diagnosis is made other members may be concerned about their own risk of developing the malignancy. Patient's with a new diagnosis of gynecologic malignancy had more distress than patients with a diagnosis of benign disease.[76] This distress was due to fatigue, anxiety, combined with confusion as well. The distress was time-limited and improved after a 12 month period. However, sexual dysfunction was significant, especially when the surgeries in gynecological cancers were disfiguring.[77] However, non-sexual, affectionate desire did not seem to be affected.[78].

Quality of life assessment in ovarian cancer can evaluate various treatments that are used to potentially increase the disease-free survival by 3–4 months. This would be statistically significant when comparison of two treatment arms is made. However, if quality of life is not assessed in these studies then it would not be discovered that the patient's life did increase by 3–4 months, the patient was in hospital for a longer time, or had other problems that manifested such as severe neuropathy or persistent nausea that cause the quality of life to be very poor. When studies are constructed that do not look at these issues then these entities are not discoverable. When severe neuropathy on taxol was combined with cisplatin over a short infusion, it would only have been picked up if a persistent investigation of quality of life was done, as described by Connelly *et al.*[79] Disease-specific states can have different instruments in evaluating quality of life.[80] When developing various therapies for ovarian cancer there is a strong need for practical clinical applications. Though editorials do at times criticize the routine inclusion of quality of life evaluations in trials,[87] the basic tenets and importance of including this would reflect uncovering the truth of various therapies in ovarian cancer. Faced with limited life expectancy, would the increase in life gained by the new treatments be offset by the toxicity? Bone marrow transplantations and other toxic therapies come to mind. In addition to new costs, a new perceived cost-containment treatment may actually cost more because, in the long run, it may worsen quality of life, requiring more intervention later. Future research needs to link the integral part of quality of life assessment with various treatments in ovarian cancer. This is contrary to what other studies have found.

Outcomes

Outcomes assessments in gynecological oncology as well as ovarian cancer have become more salient topics in recent years. As health care is being delivered, so is the measure of outcome because, ultimately outcome brings the various methods of treatment under scrutiny. Because of our inability to measure the patient's quality of life our choices have been misguided and an assessment of outcome has been the guide for the health care system.[82] As health care professionals, we are accountable. Though many of us feel besieged and frustrated by various forces, when we improve outcomes we improve all of health care. The challenge lies in improving outcomes in a most cost-effective manner and to not be fearful. Accountability and assessment are part of everyday practice as this becomes more universal. It becomes, therefore, prudent for the clinician to understand how outcomes can impact on gynecological malignancies.[83] Outcome measures beyond disease to disability, discomfort and dissatisfaction. It measures physical function, mental and psychological function as well as social function, general health perception, and symptom perception. Physicians feel threatened because practice guidelines remind them of 'cookbook medicine' and they are resistant to change. Costs can also be rather elusive, since certain costs that may be saved up-front may contain hidden costs that only become apparent later as more problems manifest themselves. The traditional approach to clinical medicine does not account for the actual relative cost of treatment. Alternative clinical approaches are rarely evaluated and the overall costs and benefits to society are also not assessed. The ethical issues in the patient's perception of health and satisfaction with care are rarely ever recorded. Though traditionally scientific inquiry has been that of evaluating the results of medical intervention and health care services, outcomes data are important measures of quality of health care because they are direct measures of whether medical interventions have been successful.[84] Outcome measurements differ slightly from quality of life in that they measure medical, biological, pathological and behavioral components. Resource utilization and costs are formulated in, as well as functional status, well-being, quality of life, productivity and disability. Symptoms and habits are formulated. The Society of Gynecological Oncologists has taken on endometrial adenocarcinoma as an outcome measure and the Short-Form-26 is used as an integral part of this. The self-assessment form is pivotal in understanding and getting a handle on

outcomes for this disease.[85] Though the data is preliminary, it is the way by which ovarian cancer and other gynecological malignancies will be judged in the future. An outcomes management program in gynecological oncology was set out by Morris and recently published.[86] This physician-driven outcomes management program was able to continue high quality of care while decreasing costs in gynecological oncology patients. Length of stay, laboratory utilization, as well as overall costs were significantly decreased with this program, which did not require much more effort from physicians. The basic tenet is that if we shine light on our own behavior and point the way then we will change. The physicians are given what is essentially a report card on their outcome and this will be kept confidential. Their behavior will naturally try to mimic the mean. In essence, if there is a physician with a long length of stay, that physician will be more cognizent of certain behaviors that cause this. Overall, if this physician's patients have the same outcomes as other physicians then change is inevitable. Since applying his program, Morris has been able to spread the program to thoracic and other surgical disciplines throughout the hospital.

Conclusion

Medicine has come to the realization that there is more to treatment of disease than that of the disease itself. Cancer, especially, has a wide range of effects on the patient, from fear, despair and anxiety to complete withdrawal from social and family interaction. Resolving these has much to do with healing the patient or easing the patient through the course of the disease, as does surgery, chemotherapy, radiation and other forms of treatment. It is the vital role of physicians and nurses to guard their patients against the pressures being exerted by insurers to focus only on physical treatment of the cancer itself and ignore the aftermath. Curing a patient or giving that patient a longer survival is good for building statistics, but what happens to the patient's life after diagnosis is the reality, not the statistics.

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References

1. Wingo PA, Tong T, Bolden S. Cancer statistics 1995. *CA Cancer J Clin* 1995; **45**: 8-30.
2. Silverberg E, Boring C, Squires T. Cancer statistics 1990. *CA Cancer J Clin* 1990; **40**: 9-26.
3. Parker SL, Tong T, Bolden S, *et al.* Cancer statistics 1997. *CA Cancer J Clin* 1997; **47**: 5-27.
4. Tobias JS, Griffiths CT. Management of ovarian carcinoma. *N Eng J Med* 1976; **249**: 818-23; 877-82.
5. Reed E, Janik G, Bookarman N, *et al.* High-dose carboplatinum and rh-GMCSF in refractory ovrian cancer. *Proc Am Soc Clin Oncol* 1990; **9**: 609 (abstr).
6. Hayes DM, Cvitkovic E, Golbey RB, *et al.* High dose cisplatinum diamine dichloride amelioration of renal toxicity by Manitel diuresis. *Cancer* 1977; **39**: 1372-75.
7. Salem P, Hall FW, Benjamin RS, *et al.* Clinical phase I-II study of cisdichlordiamine platinum (II) given by continuous IV infusion. *Cancer Treat Rep Response* 1978; **62**: 1553-5.
8. Willemse HB, Boonstra H, de Vries E. Chemotherapy dose-escalation with hemopoietic growth factor support in ovarian cancer. *Semin Oncol* 1994; **21**: 44-50 (suppl 16).
9. Biesma B, Vellenga E, Willemse P, *et al.* Effects of hemopoietic growth factors on chemotherapy induced myelosuppression. *Crit Rev Oncol Hematol* 1992; **13**: 107-34.
10. Alberts DS, Noel JK. Cisplatin associated neurotoxicity; can it be prevented? *Anti-Cancer Drugs* 1995; **6**: 369-83.
11. McGuire WP, Hoskins WJ, Brady MF, *et al.* A phase III trial comparing cisplatin/cytoxan and cisplatin/taxol in advanced ovarian cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 255 (abstr).
12. Mandelblatt J, Fahs M. Cost-effectiveness of cervical cancer screening for low income elderly women. *J Am Med Ass* 1988; **259**: 2409-13.
13. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Disseminated germ cell tumors; chemotherapy with cisplatinum plus Bleomycin plus either vinblastin or etoposide. *N Eng J Med* 1987; **316**: 1434-40.
14. Loehrer PJ, Elson P, Johnson DH, *et al.* Randomized trial of cisplatinum plus etoposide with or without belomycin in favorable prognosis disseminated germ cell tumors: an ECOG study. *Proc Am Soc Clin Oncol* 1991; **10**: 169-71.
15. Fishman DA, Weinstein J, Bennett C, Lurain J, Calhoun E. Perceptions of Cisplatin related toxicity among ovarian cancer patients and gynecologic oncologists. *Proc Soc Gynecol Oncol* **29**: 68 (abstr 29).
16. Oncology Nursing Society Board of Directors, Kathi M Mooney, RN, PhD, FAAN, AOCN, President. Oncology Nursing Society position paper on quality cancer care. *Oncol Nursing Forum* 1997; **24**: 951-53.
17. Anonymous. Oncology Society Nursing Society position paper on quality care. *Oncol Nursing Forum* 1997; **24**: 951-953.
18. Bland KI. Quality of life management of cancer patients. *Cancer* 1997; **47**: 194-7.
19. Mandelblatt J, Freeman H, Winczewski D, *et al.* The costs and effects of cervical and breast cancer screening in a public hospital emergency room. The Cancer Control Center of Harlem. *Am J Public Health* 1997; **87**: 1182-9.
20. Piver MS, Lele SB, Bowlow JJ. Preoperative and intraoperative evaluation in ovarian cancer malignancy. *Obstet Gynecol* 1976; **48**: 312-6.

21. Griffiths CT, Parker L. Cancer of the ovary. In: Knapp RC, Berkowitz RS, eds. *Gynecological oncology*. New York: MacMillan 1986: 333-6.
22. Jacobs I, *et al.* Multimodal approach to screening for ovarian cancer. *Lancet* 1988; **ii**: 268-72.
23. van Nagell Jr, JR, DePriest PD, Puls E, *et al.* Ovarian cancer screening in asymptomatic postmenopausal women by transvaginal sonography. *Cancer* 1991; 68450-62.
24. NIH Consensus Development Conference Panel. Ovarian cancer screening, treatment, and follow up. *NIH Consensus Statement 12*, 5-7 April, 1994.
25. Bombard AT, Fields AL, Aufox S, Ben-Yishay M. The genetics of ovarian cancer: an assessment of current screening protocols and recommendations for counseling families at risk. *Clin Obstet Gynecol* 1996; **39**: 860-72.
26. Piver MS. Routine ovarian cancer screening for a subset of at-risk women. *The Female Patient* 1997; **22**: 71-87.
27. Mettlin C, Murphy GP, Babaian RJ, *et al.* Results of five year early prostate cancer detection intervention. *Cancer* 1996; 77: 150-9.
28. Sickles EA. Quality assurance: how to audit your own mammography practice. *Radiol Clin N Am* 1992; **30**: 265-75.
29. Evans WK. Cost-effectiveness of gemcitabine in stage IV non-small cell lung cancer; an estimate using the Population Health Model lung cancer module. *Semin Oncol* 1997; **24** (2 Suppl 7): S7-56-63.
30. Covens A, Boucher S, Roche K, *et al.* Is Paclitaxel and Cisplatin a cost-effective first-line therapy for advanced ovarian carcinoma? *Cancer* 1996; **77**: 2086-91.
31. Messori A, Trippoli S, Becagli P, Tendi E. Pharmacoeconomic profile of paclitaxel as a first-line treatment for patients with advanced ovarian carcinoma; a lifetime cost-effectiveness analysis. *Cancer* 1996; **78**: 2366-73.
32. Buller R, Vasilev S, DiSaia P. CA125 kinetics: A cost-effective clinical tool to evaluate clinical trial outcomes in the 1990's. *Am J Obstet Gynecol* 1996; **174**: 1241-54.
33. Ubel P, DeKay M, Baron J, Asch D. Cost-effectiveness analysis in a setting of budget constraints. *New Eng J Med* 1996; **354**: 1174-7.
34. Etzioni R, Urban N, Baker M. Estimating the costs attributable to a disease with application to ovarian cancer. *Clin Epidemiol* 1996; **49**: 95-103.
35. Abbas F, Sert M, Rosenshein N, Zahyrak M, Currie J. Gynecologic oncology patients in the Surgical ICU: impact on outcome. *J Reprod Med* 1997; **47**: 173-8.
36. Abbas F, Sert M, Rosenshein N, Zahyrak M, Currie J. Prolonged stays of OB/GYN patients in the Surgical Intensive Care Unit: a cost-benefit analysis. *J Reprod Med* 1997; **42**: 179-83.
37. Tchekmedyian NS, Cella DF, Winn P, eds. Economical quality of life outcomes in oncology. *Oncology* 1995; **9**(11): suppl.
38. Donovan K, Samson-Fischer RW, Redmann S. Measuring quality of life in cancer patients. *J Clin Oncol* 1989; **7**: 959-68.
39. Feinstein AR. *Clinimetrics*. New Haven, CT: Yale University Press 1987.
40. Anderson RB, Testa MA. Symptom distress checklists as a component of quality-of-life measurement: comparing prompted reports by patient and physician with concurrent adverse event reports via the physician. *Drug Inf J* 1994; **28**: 89-114.
41. Lord FM. *Application of item response theory to practical testing problems.* Hillsdale, NJ: Lawrence Erlbaum 1980.
42. Ware JE Jr, Kosinski M, Keller SD. *SF-36 physical and mental health summary scales; a user's manual.* The Health Institute, New England Medical Center 1994.
43. Testa M, Simonson D. Assessment of quality-of-life outcomes. *N Engl J Med* 1996; **33**: 835-9.
44. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for the Research and Treatment of Cancer QLA-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365-76.
45. Schipper H, Glinch J, McMurray A, Lewis M. Measuring the quality of life of cancer patients. The Functional Living Index—Cancer: development and validation. *J Clin Oncol* 1984; **2**: 472-83.
46. Ware JF, Sherbourne CD. The MOS 36 Item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-83.
47. McHorney CA, Ware JF, Rogers W, *et al.* The validity and relative precision of MOS short- and long-form Health Status Scales and Dartmouth COOP Charts: results from the Medical Outcomes Study. *Med Care* 1992; **30**: 253-65 (suppl 5).
48. Campbell A, Converse PE, Rodgers WL. *The quality of American life.* New York: Sage 1976.
49. Till JE, McNeil BJ, Rush RS. Measurements of multiple components of quality of life. *Cancer Treat Symp* 1984; **1**: 177-81.
50. Bergner J, Bobbitt RA, Carter WB, Gibson BS. The Sickness Impact Profile. Development and final revision of a health status measure. *Med Care* 1981; **19**: 787-806.
51. Drummond MF, Stoddart GL, Torrance GW. *Methods for economic evaluation of health care programmes.* Oxford: Oxford University Press 1987.
52. Gelber RD, Goldhirsch A, Cavalli F. Quality-of-life adjusted evaluation of adjuvant therapies for operable breast cancer. *Ann Intern Med* 1991; **114**: 621-8.
53. Slevin MI, Plant H, Lynch D, *et al.* Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988; **57**: 109.
54. Nunnally JC. *Psychometric theory.* New York: McGraw-Hill 1967.
55. Mor V. Cancer patients quality of life over the disease course: lessons from the real world. *J Chron Dis* 1987; **40**: 535.
56. Ferrans CE. Development of a Quality of Life Index for patients with cancer. *Oncol Nursing Forum* 1990; **17**: 15-21 (suppl).
57. Granai C, Gajewski W, Falkenberry S, *et al.* Can we do more: complementing care (e.g. massage therapy, pet companionship) integrated with chemotherapy. The patient's perspective. *Proc Soc Gynecol Oncol* **29**: 68 (abstr 30).
58. Messias DK, Yeager KA, Dibble SI, Dodd MJ. Patients' perspectives of fatigue while undergoing chemotherapy. *Oncol Nursing Forum* 1997; **24**: 43-8.
59. Kalman D, Villani LJ. Nutritional aspects of cancer-related fatigue. *J Am Dietitic Ass* 1997; **97**: 650-4.
60. Erlick-Robinson G, Rosen BP, Bradley LN, *et al.* Psychological impact of screening for familial ovarian cancer; reactions to initial assessment. *Gynecol Oncol* 1997; **65**: 197-205.

61. Hack TF, Degner LF, Dyck DG. Relationship between preferences for decisional control and illness information among women with breast cancer: a quantitative and qualitative analysis. *Soc Sci Med* 1994; **39**: 279–89.
62. Bennahum DA, Forman WB, Vellas B, Albarede JL. Life expectancy, co-morbidity, and quality of life. A framework of reference for medical decisions. *Clin Geriat Med* 1997; **13**: 33–53.
63. McMillan SC. The quality of life of patients with cancer receiving hospice care. *Oncol Nursing Forum* 1996; **23**: 1221–8.
64. Larsen J, Gardulf A, Nordstrom G, Bjorkstrand B, Ljungman P. Health-related quality of life in women with breast cancer undergoing stem cell transplantation. *Cancer Nursing* 1996; **19**: 368–75.
65. Wyatt G, Friedman LL. Long-term female cancer survivors: quality of life issues and clinical implications. *Cancer Nursing* 1996; **19**: 1–7.
66. Smith SL. Physical exercise as an oncology nursing intervention to enhance quality of life. *Oncol Nursing Forum* 1996; **23**: 771–8.
67. Kosmidis P. Quality of life as a new end point. *Chest* 1996; **109** (5 suppl): 110S–2.
68. Constitution of the World Health Organization. In: *World Health Organization. Handbook of basic documents*, 5th edn. Geneva: Palais des Nations 1952: 3–20.
69. Their SO. Forces motivating the use of health status assessment measures in clinical settings and related clinical research. *Med Care* 1992; **30** (suppl): MS15–22.
70. Patrick DL, Bush JW, Chen MM. Toward an operational definition of health. *J Health Soc Behav* 1973; **14**: 6–23.
71. Brook RH, Ware JE Jr, Rogers WH, *et al.* Does free care improve adults' health? Results from a randomized, controlled trial. *N Eng J Med* 1983; **309**: 1426–34.
72. Bergner M. Quality of life, health status, and clinical research. *Med Care* 1989; **27** (suppl): S148–56.
73. Patrick DL, Erickson P. Concepts of health-related quality of life. In: Patrick DL, Erickson P, eds. *Health status and health policy; quality of life in health care evaluation and resource allocation.* New York: Oxford University Press 1993: 76–112.
74. Anderson B, Lutgendorf S. Quality of life in gynecologic cancer survivors. *CA Cancer J Clin* 1997; **47**: 218–225.
75. Anderson B, LaPolla J, Turner D, *et al.* Ovarian transposition in cervical cancer. *Gynecol Oncol* 1993; **49**: 206–14.
76. Anderson BL, Lachenbruch PA, deProsse C. Controlled prospective longitudinal study of women with cancer II: psychological outcomes. *J Consult Clin Psychol* 1989; **57**: 692–7.
77. Anderson BL, Anderson B, deProsse C. Controlled prospective longitudinal study of women with cancer: I. Sexual functioning outcomes. *J Consult Clin Psychol* 1989; **57**: 683–91.
78. Anderson BL, Lachenbruch PA, Anderson B, *et al.* Sexual dysfunction and signs of gynecologic cancer. *Cancer* 1986; **57**: 1880–6.
79. Connelly E, Markman M, Kennedy A, *et al.* Paclitaxel delivered as a 3-hr infusion with cisplatin in patients with gynecologic cancers: unexpected incidence of neurotoxicity. *Gynecol Oncol* 1996; **62**: 166–8.
80. Hergner M, Bobbitt RA, Carter WH, Gibson BS. The sickness impact profile: development and final revision of a health status measure. *Med Care* 1981; **19**: 787–805.
81. Erlick-Robinson G, Rosen BP, Bradley LN, *et al.* Psychological impact of screening for familial ovarian cancer; reactions to initial assessment. *Gynecol Oncol* 1997; **65**: 197–205.
82. Ellwood P. Outcomes management: a technology of patient experience. The Shattuck Lecture. *N Engl J Med* 1988; **318**: 1549–56.
83. Relman A. Assessment and accountability: the third revolution in medicine. *N Engl J Med* 1988; **319**: 1220–2.
84. Reemtsma K, Morgan M. Outcomes assessment: a primer. *Bull Am Coll Surg* 1997; **82**: 34–9.
85. Kennedy AW. Outcomes management: an opportunity for our future. *Gynecol Oncol* 1996; **63**: 157–8.
86. Morris M, Levenback C, Burke T, Dejesus Y, Lucas K, Gershenson D. An outcomes management program in gynecologic oncology. *Obstet Gynecol* 1997; **89**: 485–92.