CHAPTER 1

INTRODUCTION
The focus of this thesis is an economic evaluation of short-term $5 \times 5$ Gy preoperative radiotherapy (PRT) in patients with rectal cancer undergoing total mesorectal excision (TME). The study was conducted alongside a randomized clinical trial, the TME-study, and was designed to address additional clinical and methodological issues. This chapter provides a general introduction on the treatment of rectal cancer and the TME-trial, and on economic evaluations in health care. The chapter concludes with an outline of this thesis and short rationale for each study presented in this thesis.
Rectal cancer and the TME-trial

In Europe and the United States, colorectal cancer is the 2nd most common cancer after lung cancer, and about 5% of the population will personally be confronted with colorectal cancer during their lifetime (1;2). In the Netherlands, in 1995, about 8000 patients were diagnosed with colorectal cancer, of which 25% had rectal cancer (2).

For both colon and rectal cancer, surgical resection of the primary tumor is the predominant treatment option. Successful surgery of a rectal tumor is more difficult than potentially curative surgical removal of a colon tumor due to the presence of the bony pelvis and other vital organs. Therefore, in rectal cancer the focus has been on the prevention of local recurrences by improving surgical techniques and locally adjuvant pre- or postoperative radiotherapy, whereas in colon cancer the focus has been on the prevention of metastatic disease by adjuvant chemotherapy treatment (3).

In rectal cancer, total mesorectal excision (TME) is now the preferred surgical technique. The aim of this technique is complete removal of the mesorectum (i.e. the rectum including the surrounding fatty lymphovascular tissue) with negative resection margins by sharp dissection and under thorough inspection of the pelvis and the pelvic autonomic nerves (4;5). Conventional surgery often implied blunt dissection of part of the rectum, resulting in positive resection margins. In the Netherlands, TME-surgery was introduced by the Dutch Colorectal Cancer Group, using an extensive structure of workshops, symposia, and trained instructor surgeons (6). A randomized comparison of TME-surgery versus conventional surgery was considered unethical, because the improvement of TME-surgery over conventional surgery was beyond doubt. Recent literature indeed showed that the introduction of TME-surgery has reduced local recurrence rates from 15%-45% to 5%-8%, and that 5-year survival has increased from 49% to 61% (7-12).

The additional value of adjuvant radiotherapy to prevent local recurrence rates in combination with conventional surgery was shown in several Swedish studies, with short-term preoperative radiotherapy (5×5 Gy) being more effective than postoperative radiotherapy or long-term radiotherapy schedules (13-15). Preoperative short-term radiotherapy inhibits the proliferation of well-oxygenated tumor cells, and reduces the risk of repopulation of tumor cells that may occur using longer schedules with longer overall treatment times (16). After surgery, because of changed vascularisation, tumor cells may be less well oxygenated, which may explain why preoperative radiotherapy schedules are more effective than postoperative schedules (16).

In conclusion, both TME-surgery and short-term preoperative radiotherapy (PRT) have independently been shown to reduce local recurrence rates. The question whether 5×5 Gy PRT would still have a beneficial effect in combination with TME-surgery was recently answered by the TME-trial, a multicenter randomized clinical trial conducted by the Dutch Colorectal Cancer Group (6). At 2 years follow-up the estimated local recurrence rate was 2.4% with PRT, as compared with 8.2% without PRT. However, the current follow-up does
not show a significant survival difference between randomization groups and PRT has also been associated with higher costs and increased postoperative morbidity (13;14;17-22). Therefore, secondary objectives of the TME-trial were to assess quality of life and cost-effectiveness.

**Cost-effectiveness analyses**

Over the last decades, economic evaluations of health care have gained increasing attention for various reasons. The large amounts of money involved in health care (in the Netherlands, in 2002, about 52 billion Euro, 11.5% of the gross domestic product, was spent on health care(23)), the rise in available medical technologies, the increasing population age, the awareness that health care interventions may not always promote quality and length of life, and society's call for greater accountability have all raised questions about the appropriateness and efficiency of health care. Economic evaluations can provide information on the costs and consequences of health care interventions. This information may help policy makers in deciding how to allocate health care resources, provide evidence for clinical guidelines, and promote the transparency of health care.

There are several types of economic evaluations, that differ by the way in which the consequences of health care interventions are taken into account. Cost-effectiveness analysis is the most extensive type of economic evaluation, explicitly comparing the costs and consequences of two or more alternative courses of action, e.g., a comparison of a mammographic screening program versus 'doing nothing' in the early detection of breast cancer (24-26). Health outcomes are measured in natural or physical units, e.g. detected cases of breast cancer, prevented strokes, blood pressure reductions, or life years gained. The economic value of two alternative interventions is compared by dividing the difference in costs between the alternatives by the difference in health outcomes (27). Thus, the aim of cost-effectiveness analysis is not just to minimize costs, but is to provide information on the value-for-money or so-called incremental cost-effectiveness, that is the additional costs needed to obtain additional health gains.

Cost-utility analysis is a specific form of cost-effectiveness analysis, in which the effects of health care interventions on life years and quality of life are estimated and combined in a single outcome measure: quality adjusted life years or QALYs (27). To calculate QALYs, a description of quality of life alone is not sufficient, and information is needed on the utility or valuation of that quality of life. For example, a patient may report fatigue after chemotherapy for cancer (description), but may not be willing to trade-off longer life expectancy to avoid this fatigue (valuation). Utility is measured on a scale from 1 (health state valued equal to perfect health) to 0 (health state valued equal to death), or even less than 0 (for health states valued worse than death) (28). The use of QALYs in economic analyses implies that health care interventions that improve survival, but also have negative effects on quality of life are not necessarily considered effective. The gain in life years may no longer render a gain in QALYs if people are willing to trade-off survival to obtain better quality of life.
Ideally, the use of a generic measure such as QALYs in economic evaluations enables the comparison of results over different health care interventions and patient populations. The idea of comparing the cost-effectiveness of an intervention to a consensus-based acceptability threshold is appealing, since this would greatly facilitate decision making on the distribution of health care resources (29;30). Indeed, one would only have to know whether the cost-effectiveness ratio of a health care intervention is below or above the determined threshold. However, in addition to the difficulties in determining an acceptability threshold (29), there are at least two other problems for policy makers. First, the cost-effectiveness ratio is rarely the only decision criterium, and other criteria often play a more important role (29;31), e.g. overall costs, the public's opinion, scientific developments, commercial interests and moral dilemmas (32). Second, the methodology used to assess costs and effects of health care interventions ranges widely, hampering the comparability of study results.

In several countries, guidelines have been developed to standardize and improve the methodology of cost-effectiveness studies (27;33;34). Most guidelines state that cost-effectiveness analyses should be performed from a societal perspective. This implies that all medical costs (e.g. treatment costs, costs of complications, medication costs), non-medical costs (e.g. productivity costs, informal care, out-of-pocket expenses), and health effects that are significantly affected by the intervention should be included, irrespective of who pays for or benefits from those costs or health effects.

An increasing number of economic evaluations are performed as ‘piggyback’ studies alongside clinical trials. Clinical trials are the clinical gold standard for evaluating effectiveness and also provide the best guarantee of internal validity for the comparison of costs and quality of life. However, the sample sizes needed to compare clinical outcomes (e.g. 5-year recurrence rates) may not provide sufficient power to compare costs and quality of life, and clinical trials may have limited external validity or generalizability (35;36). In addition, the time horizon of clinical trials is usually limited to the time during which most clinical events can occur, whereas for economic evaluations patients may need to be followed until death. To overcome these problems, decision analytic modelling is frequently applied in economic evaluations. Decision models allow for the integration of all available data from clinical trials, and facilitate long-term extrapolation and sensitivity analyses (i.e. analysis of the sensitivity of cost-effectiveness to changes in model parameters) (37).

**Outline of this thesis**

The focus of this thesis is the cost-utility analysis of 5×5 Gy PRT combined with TME-surgery in patients with rectal cancer. The cost-utility analysis was performed alongside the TME-study and was designed to address additional clinical and methodological issues.

Chapter 2 of this thesis presents the results of a literature review on cost-effectiveness analyses of colorectal cancer. The first part of this chapter discusses the methodology of cost-effectiveness analyses in more detail and highlights some of the choices to be made in
the design of a cost-effectiveness analysis. The second part of this chapter provides an overview of published cost-effectiveness studies on the treatment and follow-up of colorectal cancer.

In chapter 3, the main study of this thesis, the cost-utility analysis of PRT in patients with rectal cancer undergoing TME-surgery, is presented. Data on local recurrence rates, quality of life, and costs were obtained from patients participating in the TME-trial and integrated in a decision analytic model to compare the societal costs and the quality adjusted life expectancy of patients treated with or without PRT.

In chapters 4 and 5 two more clinical issues are addressed. Chapter 4 presents the results of a longitudinal study on the impact of PRT in combination with TME-surgery for paid and unpaid labour. Over the last decades, new treatment techniques have reduced recurrence rates and improved survival for many types of cancer (38;39). This has increased the interest in the societal reintegration of survivors of cancer, since for many patients cancer is no longer an incurable and fatal disease (40). In addition, new treatment techniques may also change the prognosis after a local recurrence (41;42). Updated information on the follow-up after recurrence diagnosis is therefore clinically relevant and also affects estimated cost-effectiveness. In chapter 5, the clinical nature and prognosis of locally recurrent rectal cancer is described for patients treated with or without PRT for the primary tumor, and explanations for the difference in survival after local recurrence are explored.

Chapters 6 to 8 highlight some methodological issues concerning the assessment of costs and utilities alongside clinical trials. Traditionally, published estimates have been most frequently used to assess costs in economic evaluations of health care (43). However, these estimates often are not very specific and cannot be found for all relevant costs (e.g. non-hospital costs, personal care products). As an alternative, both providers of care and patients may be used as primary data sources, each with their own (dis)advantages. In chapter 6, the results of a within-subjects study on the feasibility and convergent validity of providers’ and patients’ reports for the assessment of health care utilization are presented. Chapter 7 presents a study in which the comparability of two measurement methods, a cost diary and a cost questionnaire, was prospectively compared in two separate samples of patients. Self-administered questionnaires or diaries are not considered suitable for the assessment of utility values or preferences. The elicitation of preferences requires personal interviews with well-trained interviewers to overcome problems related to the understanding and interpretation of those questions (44-46). Chapter 8 presents the results of a randomized study in which the feasibility and convergent validity of telephone interviews, as compared to face-to-face interviews, for the assessment of costs, quality of life and preferences was investigated.

Finally, in chapter 9, the main conclusions of this thesis are described and the findings of the previous chapters are discussed.
References


(23) Statistics Netherlands (www.staline.cbs.nl), 2001


(29) Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med 2003; 163(14):1637-1641.