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Quality of life and cost effectiveness in a randomized trial of patients with colorectal cancer and peritoneal metastases

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ABSTRACT

Background: The aim was to compare health-related quality-of-life (HRQOL) and cost-effectiveness between cytoreductive surgery with intraperitoneal chemotherapy (CRS + IPC) and systemic chemotherapy for patients with colorectal peritoneal metastases.

Methods: Patients included in the Swedish Peritoneal Trial comparing CRS + IPC and systemic chemotherapy completed the EORTC QLQ-C30 and SF-36 questionnaires at baseline, 2, 4, 6, 12, 18, and 24 months. HRQOL at 24 months was the primary endpoint. EORTC sum score, SF-36 physical and mental component scores at 24 months were calculated and compared for each arm and then referenced against general population values. Two quality-adjusted life-year (QALY) indices were applied (EORTC-8D and SF-6D) and an incremental cost-effectiveness ratio (ICER) per QALY gained was calculated. A projected life-time ICER per QALY gained was calculated using predicted survival according to Swedish population statistics.

Results: No statistical differences in HRQOL between the arms were noted at 24 months. Descriptively, survivors in the surgery arm had higher summary scores than the general population at 24 months, whereas survivors in the chemotherapy arm had lower scores. The projected life-time QALY benefit was 3.8 QALYs in favor of the surgery arm (p=0.06) with an ICER per QALY gained at 310,000 SEK (EORTC-8D) or 362,000 SEK (SF-6D) corresponding to 26,700–31,200 GBP.

Conclusion: The HRQOL in patients with colorectal peritoneal metastases undergoing CRS + IPC appear similar to those receiving systemic chemotherapy. Two-year survivors in the CRS + IPC arm have comparable HRQOL to a general population reference. The treatment is cost-effective according to NICE guidelines.

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Introduction

Treatment of colorectal cancer with peritoneal metastases has changed over the past years and isolated peritoneal metastases are presently considered as loco-regional disease amenable to curative treatment [1]. The combination of cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) has been evaluated in two randomized trials revealing a survival benefit for CRS + IPC and several observational studies demonstrate long-term cure [2–5]. These studies have evaluated CRS in conjunction with several different IPC methods: hyperthermic intraperitoneal chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), sequential postoperative intraperitoneal chemotherapy (SPIC). Despite these and other comparative studies demonstrating a benefit of CRS + IPC [6–8], controversy lingers with about 50% of oncologists considering it a standard treatment option [9]. A major problem is morbidity, and few studies have analyzed morbidity after CRS + IPC compared with systemic chemotherapy. The first randomized trial didn't report morbidity of the chemotherapy arm, only of the surgery arm [2], whereas in the Swedish Peritoneal Trial grade III-IV adverse events were seen in 50% of patients in the chemotherapy arm vs. 42% in the surgery arm [3]. This indicates

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that systemic chemotherapy is toxic in patients with peritoneal metastases. Concerns for postoperative complications resulting in impaired quality-of-life are important factors leading to skepticism of CRS + IPC. Moreover, there are no comparative health-related quality-of-life (HRQOL) studies or any cost-effectiveness studies within this field. The aims of this study were to compare the HRQOL and cost-effectiveness from the Swedish Peritoneal Trial using the CRS + SPIC approach.

Patients and methods

Participants

This was an open-label multi-center randomized study between the surgery arm and the chemotherapy arm for the treatment of isolated colorectal peritoneal metastases. The surgery arm consisted of CRS treatment followed by repeated sequential postoperative intraperitoneal chemotherapy (SPIC) once-a-month for 6 months using 5-flourouracil 550 mg/m^2. The systemic chemotherapy arm had no planned initial surgery and received oxaliplatin-based systemic chemotherapy for 12 cycles (6 months). More details about the participants and the SPIC method have been published [3]. The study was registered at ClinicalTrials.gov (NCT01524094) and approved by the regional ethical review board at all participating centers.

Randomization and trial methodology

Full details of randomization and trial methodology have been published [3]. In summary, 48 patients were included, 24 patients/arm. The primary endpoint was survival at 2 years. The patients were followed up the first 2 years with iterative CT scans. Thereafter, the follow-up was according to clinical routine with study follow-up ending on March 1st, 2016.

Quality of life and missing data management

Two validated questionnaires were used for quality-of-life assessment – SF 36 and EORTC QLQ-C30 [10–13]. Both questionnaires were completed before randomization and after 2, 4, 6, 12, 18, and 24 months. Random single missing data items or single missing questionnaires were handled by the last observation carried forward method [14,15]. If a patient died prior to the two-year follow-up, the patient was judged complete, if all questionnaires up to the point-of-death were completed. The quality-of-life scores were set to the worst possible score after the date of death for the remaining time points until the 2-year follow-up.

The primary analysis included the complete cases (n = 34) and was complemented by three “intention-to-treat” sensitivity analyses on all 48 cases: (1) last observation carried forward method, (2) all missing data set to worst possible value, (3) median value of the whole study group set for each particular time point. One subset analysis excluding deceased patients was performed in order to measure actual HRQOL levels between the arms at 24 months without death scores affecting the outcome. The following summary scores were used and referenced to the general population: EORTC sum score, SF-36 physical component score (PCS), and SF-36 mental component score (MCS).

Cost-effectiveness

The cost-effectiveness analysis was pre-planned in the protocol. Primary therapy in both arms spanned over 6 months. Due to a cross-over option, treatment costs were calculated from randomization until completed primary therapy. If a patient didn't complete primary therapy and was referred for secondary treatment earlier, costs were registered until secondary therapy started. Results from the SF-36 and EORTC QLQ-C30 were converted to standard gamble SF-6D index and EORTC-8D index, respectively, for quality-adjusted life-years (QALY) assessment [16–18]. Conversions were conducted using Microsoft Excel sheet programming or SPSS programming provided by the University of Sheffield on a non-profit license. QALY analysis was performed for the full 7-year follow-up. A standard cost chart was developed and applied to all patients regardless of center: operating costs/min, hospital admission costs, standard costs of epidural and patient-controlled analgesia pumps, costs/hour in the intensive care unit, costs/day in the surgical ward (including standard lab-work and medications), costs for radiology, outpatient clinic/visit, chemotherapy, anti-emetics and other drugs received. Costs were individually evaluated for complications for both arms (including reoperations, prolonged total parenteral nutrition costs, radiological interventions, readmission to the hospital, other necessary medical interventions). A projected estimate of life-time QALY benefit was calculated.

Statistics

Primary outcome of the HRQOL analysis was defined at the 24-month follow-up for the complete cases (n = 34). The three sensitivity analyses were calculated with the Mann-Whitney-U test at 24 months. Two calculations were made, one with all patients and one excluding deceased patients as a subset analysis. Reference mean values from a general population were added. Validated sum scores were applied – EORTC sum score [19], SF-36 PCS, and SF-36 MCS [20]. Repeat-measure ANOVA and Kruskal-Wallis tests were performed on each comparable HRQOL domain for both the EORTC QLQ-C30 and the SF-36 questionnaires.

The mean QALY benefit/arm was calculated using the area-under-the-curve (AUC) of the QALY indices (standard gamble SF-6D and EORTC 8D) for each patient from baseline to two years. Between two and seven years, the last QALY index (SF-6D and EORTC 8D) at 24 months was carried forward until death at which point the index fell to zero. The AUC from the first two years was added to the imputed AUC from two to seven years to get a total QALY value for the seven-year observation time. The mean QALY difference between the arms was calculated by Mann-Whitney-U test. Health costs/patient and mean difference between arms were calculated. Using mean QALY difference and mean cost difference, an incremental cost-effectiveness ratio (ICER) per gained QALY was calculated. A 3.5% discount rate/year of the QALY benefit was applied according to NICE guidelines [21].

Remaining life-years expected from the seven-year follow-up point could be estimated using statistics from Sweden's Central Bureau of Statistics (Statistiska Centralbyrån) using birth date, age at the seven-year follow-up, and gender as predictors. This was applied to the four patients deemed cured after seven years follow-up. These patients were expected to follow their predicted life-expectancies. QALY calculation using QALY indices from the 24-month time point was used to adjust the estimated remaining life-years. An ICER per gained QALY for both arms was calculated with a 3.5% discount rate until the last patient's expected life-year. Statistics were calculated with the Statistica software v12. A p-value < 0.05 was considered statistically significant.

Results

Questionnaire response rate and survival update

For details on response rates see Table 1. Thirty-four (71%) of 48 patients completed the entire HRQOL follow-up. Reasons for

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