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Title

Referral Pathways and Outcome of patients with colorectal peritoneal metastasis (CRPM).

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ABSTRACT

Introduction: Traditionally patients with colorectal peritoneal metastases (CRPM) were offered palliative chemotherapy and best supportive care. With the introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), patients in the UK have been referred to nationally approved centres. This study describes the pattern of referral and outcomes of patients managed through one UK centre.

Methods and Methods: A prospective register recorded referrals, demographics, prior treatment pathways, and specialist multidisciplinary team (MDT) decisions (2002-2015). Peritoneal cancer index (PCI) was recorded intra-operatively; complete cytoreduction was deemed when a CC0/1 was achieved. Complications were classified using NCI CTCAE.v.4. Median overall survivals (OS) were described for those treated by CRS/HIPEC and in derived estimates for patients with isolated peritoneal metastases treated by chemotherapy alone in the ARCAD trials consortium.

Results: Two-hundred-eighty-six patients with CRPM were referred. Despite increasing numbers of referrals annually, the proportion of patients selected for CRS/HIPEC decreased from 64.5%, to 40%, and to 37.1% for 2002-09, 2010-12, and 2013-15, respectively ($p<0.017$). CRS/HIPEC was undertaken in 117 patients with a median PCI of 7 and CC0/1 achieved in 86.3%. NCI CTCAE grade 3/4 complication rates were 9.4%; 30-day mortality was 0.85%. Median OS following CRS/HIPEC was 46.0 months: that for patients not receiving CRS/HIPEC was 13.2 months.

Conclusion: The evolution of the national peritoneal treatment centre over 14 years has been associated with increased referral numbers, refinement of selection for major surgery, matched with achievements of low complication rates and survival advantages in selected patients compared with traditional non-surgical treatments.

Key words: Colorectal peritoneal metastases (CRPM), cytoreductive surgery (CRS), heated intraperitoneal chemotherapy (HIPEC).

1. Introduction

The term colorectal peritoneal metastases (CRPM) is the preferred one for peritoneal carcinomatosis (PC) of colorectal origin[1]. Over the last two decades, treatment for liver metastases has become the accepted standard of care converting patients from a palliative to potentially curative path[2]. Similar approaches to peritoneal metastases are now possible and in the UK cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has been accepted as a treatment in selected patients (Table 1)[3].

CRPM can present synchronously (10.3% of primary right colon cancers, 6.2% of left colon cancers, and 27% of rectal cancers) and metachronously (20% of colorectal cancers), with as many as 50% of cases demonstrating isolated disease at the time of presentation[4–9]. In the Sweden National Cancer Registry, CRPM synchronous or metachronous metastases were present in 8.3% of colorectal cancer patients and were the sole site of metastasis in 4.8% of the cases[10]. Given that in 2012 more than 400,000 new colorectal cancer (CRC) cases were recorded in Europe, the burden of colorectal peritoneal disease (CRPM) has a significant impact on health services[11].

Historically, the occurrence of PM originating from adenocarcinomas of non-gynecologic primary carried a poor prognosis[8,9]. Even with current systemic chemotherapy regimes, the outcome remains disappointing, with median overall and disease free survival of 30 and 10 months, respectively[12–15]. A recent editorial raised concerns at the lack of information regarding outcomes of CRPM patients undergoing systemic anticancer treatments and the lack of enrolment of this group of patients in clinical trials[16].

For CRPM, systemic chemotherapy and palliative support used to be the mainstay of treatment, with surgery restricted to relieving obstruction. In the last decade however, compelling data on outcomes following CRS/HIPEC from several specialist centres has emerged[2,17–22]. These studies have shown a median survival of 22.3 to 63 months and a 5-year survival of up to 51% is achievable with CRS/HIPEC, in a highly selected group of patients, compared to 12 to 24 months

and up to 13% for matched patients receiving systemic chemotherapy alone [2,17,18,22,23]. More recently guidelines from the European Society of Medical Oncology recommend CRS/HIPEC for selected cases of CRPM[12].

Over the last decade, CRS and HIPEC for CRPM patients has been adopted by a number of groups and published series includes a randomised controlled study, a multicentre study, case series retrospective analysis, and a systematic review and meta-analysis[2,17,22,24–26]. Based on this evidence, CRS/HIPEC has been adopted for CRPM by several centers worldwide. Unfortunately, there has been little regulation regarding the introduction of CRS/HIPEC resulting in a wide variation in selection for treatment, early and late outcomes and scepticism from many in the non-surgical oncological arena regarding its effectiveness. In a bid to define guidelines for treatment, a consensus was proposed and adopted by the Peritoneal Society of Oncology Group International (PSOGI) in 2015[16].

Delivery of specialist healthcare in the UK has supported the introduction of a programme of CRS/HIPEC, which has resulted in cohorts of patients being referred to national registered centres. This study aims to evaluate the trends in referral and outcomes of treatment of CRPM at one of the national peritoneal tumour centres (The Christie Hospital, Manchester).

2. Methods

2.1 Patients

Institutional clinical audit review board approval was obtained. A prospectively collected database was used to identify patients with CRPM referred to the Colorectal and Peritoneal Oncology Centre (CPOC) at The Christie Hospital National Health Service Foundation Trust, Manchester (UK) between 2002 and June 2015.

In 2013 the NHS England Commissioning Board agreed selection criteria for treatment of CRPM (Table 1). Each patient was assessed through dedicated specialist multidisciplinary team (MDT) meetings comprising of a core membership of colorectal and hepatobiliary surgeons, medical

oncologists, radiologists, pathologists, and Clinical Nurse specialists all with expertise in peritoneal surface malignancy (PSM). For each case, clinical records, prior treatments, pathology review, radiologic examinations, and tumor marker measurements were recorded. The MDT allowed the complete assessment of individual cases and considered the potential treatment options concluding in a management package customised to the individual patient circumstances. For patients undergoing CRS/HIPEC the intraoperative findings, Peritoneal Cancer Index (PCI) and completeness of cytoreduction (CC) scores were recorded; PCI by definition is an intraoperative index of disease burden and hence was captured at the time of surgery in patients undergoing CRS. Although the concept of a radiological PCI at MDT is an attractive one, and has more recently been adopted in some centres this was not standard practice during the study period. Even to date there is no universally accepted and validated pre-treatment PCI scoring system. The reasons for rejecting patients for CRS/HIPEC included extent of peritoneal disease such that CC0/1 was unlikely to be achieved, active systemic disease, progressive disease on chemotherapy, and being unfit for surgery. The postoperative morbidity and mortality was recorded using the National Cancer Institute Common Terminology Criteria for Adverse Effects (NCI CTCAE), version 4.0[27].

2.2 Treatment

All patients underwent general anaesthesia with central and arterial monitoring for haemodynamic, oxygenation and renal function evaluation during surgery. Wherever possible and in 90% of patients, epidural catheters were inserted to maximise postoperative pain management.

CRS included visceral resection of involved organs and peritonectomy procedures as required adopted from that described by Sugarbaker[28]. Peritoneal disease burden was assessed intraoperatively using the PCI, which yields scores ranging from 0 to 39[29,30]. In all cases, the objective was to achieve a complete cytoreduction of macroscopic disease[28]. Completeness of disease removal was determined intraoperatively using the CC scoring system[31]. A score of CC0 indicates no residual disease, CC1 indicates nodules less than 2.5 millimetres remaining, CC2

indicates nodules between 2.5 millimetres and 2.5 centimetres remaining, and CC3 reflects nodules greater than 2.5 centimetres remaining. Where scores CC0 and CC1 were achieved, patients were classified as having a complete cytoreduction.

HIPEC was delivered using a semi-closed modification of the Coliseum technique[32,33]. In the semi-closed technique, temperature probes are positioned into four quadrants to ensure equilibration of temperature during HIPEC delivery. The abdomen was filled with 2 l/m^2 of 1.5% dextrose peritoneal dialysis solution (Dianeal, Baxter Healthcare Corporation, Deerfield, IL) prior to the introduction of 35 mg/m^2 mitomycin C in three pulses at 30 minute intervals for a total of 90 minutes at a temperature of 42°C, using the Performer® LRT system (RanD, Medolla, Italy). Alternatively, a bolus iv administration of of folinic acid (calcium folinate) 50 mg was followed by 400 mg/m^2 5-flurouracil (5FU) iv administration over an hour, which was followed by 368 mg/m^2 oxaliplatin intra-peritonealy for 30 minutes. The oxaliplatin dose was selected after reviewing the protocols of other providers at that time and decided on a reduced dose as due to possible complications without additional benefit. The use of mitomycin C or oxalipatin was determined from the patient's prior chemotherapy treatments and related side effects. Following the intraperitoneal drug perfusion, the abdomen was washed with saline over 10 minutes.

2.3 Postoperative Management and Follow-Up

After the procedure, patients were transferred to the critical care unit (CCU), for monitoring, and support. All patients self ventilated within two hours of anaesthetic reversal. Patients remained on CCU until fluid balance, haemodynamics and pain control were deemed stable prior to transfer to the surgical ward for recovery. Patients were followed-up every 6-months for 2 years after CRS/HIPEC and annually thereafter, with CT chest/abdomen/pelvis at 6, 12, 18, 24, 36, 48, 60, and 96 months accompanied by tumour markers (serum CEA, Ca125, and Ca19.9).

2.4 Statistical Analysis

Statistical analyses were performed using Stata® 12.0 software (College Station, TX). We described changes over time as proportions per time periods and tested for trends using chi-squared. Median overall survival was estimated using Kaplan-Meier (K-M) tables.

To describe survival in patients selected to undergo CRS/HIPEC versus survival in patients with isolated peritoneal metastases treated by chemotherapy alone, we captured survival estimates from the published analysis and research in cancers of the digestive system (ARCAD) database using Engauge Digitizer, a validated software that captures published K-M curve images, and with known baseline sample sizes, derives individual-level data. From these two groups, we report median survivals but deemed it not appropriate to statistically compare[23,34].

3. Results

The study consists of data from 286 patients with a confirmed CRPM diagnosis. The mean age of the study population was 57.7 years and 50.3% were males. Over time there was a significant increase in referrals/year (range: 1 – 80) (Figure 1). The MDT recommended against CRS/HIPEC in 169 (59.1%) patients (Figure 2) due to: extent of peritoneal disease such that CC0/1 was unlikely to be achieved (40.5%), active systemic disease (28.6%), progressive disease on chemotherapy (11.3%); and being unfit for surgery (9.5%). Seven patients refused CRS/HIPEC when offered (4.2%).

There was variation over time with respect to MDT recommendations (Figure 3). During the period 2002-2009, the MDT recommended CRS/HIPEC in 64.5% of CRPM referrals. This percentage decreased to 40% and 37.1% during the 2010-2012 and 2013-2015 periods, respectively. This was a statistically significant difference ($p<0.017$).

Of the 40.9% (n=117) of patients who underwent CRS/HIPEC, there was a median PCI of 7 (range: 0-31). Forty-one (35%), 28 (24%), 32 (27%), and 11 (9%) patients had PCI range score of 0-5, 6-10, 11-21, and 22-31, respectively. There were no PCI score data for 5 patients. Complete cytoreduction (CC0/1 score) was achieved in 86.3% (n=101). The mean CCU stay was 2.91 (±0.55)

days and the mean hospital stay was 10.55 (±0.38) days. Combined grade 3/4 complication rate was 9.4% (n=11) and the 30-day mortality rate was 0.85% (n=1).

In terms of gender, age, referral region, time from CRPM diagnosis to referral, referral team / physician (i.e. surgical team, medical oncology team, general practitioner, self referral), and timing of CRPM diagnosis (i.e. before the 1st operation, at the 1st operation, later during follow-up) there were no differences between patients where CRS/HIPEC was offered and not. Equally, there were no differences in terms of pre-referral operation status and number of prior surgical interventions, pre-referral chemotherapy treatments, duration of the 1st pre-referral chemotherapy, and total duration of pre-referral chemotherapies.

Pre-referral radiotherapy was offered to 2.4% of the patients that did not undergo CRS/HIPEC and to 8.6% of the patients that the MDT advised for surgery (p=0.024).

Median overall survival (OS) following CRS/HIPEC was 46.0 months; for patients not undergoing CRS/HIPEC median survival was 13.2 months (Figure 4). Also included is the derived survival from the ARCAD database study. Table 2 presents the results in our study along with other equivalent non-randomised comparative studies. The OS for patients that received CRS/HIPEC had no statistically significant correlation with time from diagnosis to referral, referral period group, and referral team.

4. Discussion

Although there have been a number of case series addressing activity and outcomes following CRS/HIPEC for CRPM, this is among the very few studies that explore the patient pathway and describes outcomes for the complete cohort of referrals including those not undergoing surgery and those considered not suitable for CRS/HIPEC[35]. It is notable that over the period of this study, health service directives have facilitated an increase in referrals and increased awareness of CRS/HIPEC for patients with CRPM. In mainland Europe, the delivery of CRS/HIPEC varies in different countries, but in general is less regulated than in the UK. In England to date, only three

providers are commissioned to offer this service for a population of 53 million. Although this has the advantage of standardising treatment in high volume centres it presents challenges of access and timely delivery of treatments for this patient group. The data from this analysis assists in identifying appropriate patients for consideration by specialist MDT's and sets a benchmark for delivering a quality service and achieving best outcomes for patients, restricting the provision to too few centres may limit equity of access to treatment for appropriately selected patients.

This study presents the experience of a single specialist MDT and the ability to identify criteria for selection of patients for CRS/HIPEC. The increasing number of referrals could possibly reflect both the effect of the disease and the availability of the treatment becoming better known over the last five years. It is notable that overall almost 60% of patients were deemed unsuitable for CRS/HIPEC but perhaps more crucially, the percentage of the cases where the MDT advised against surgery increased from 30 to 60% over time. This is a reflection of improved discrimination by the MDT in parallel with assimilation of experience within the team and from others working in the field. For example, awareness that PCI as a key discriminator for achieving complete cytoreduction in CRPM has come to the fore over the last five years with consensus guidelines recommending an objective of complete CRS for this group of patients[16, 36–38]. In this series, a complete cytoreduction (CC0/1) was achieved in 86.3% of patients undergoing surgery. This percentage is among the highest of corresponding reported series[2,25,39,40].

The achievement of high levels of cytoreduction (>86% CC0/1), low morbidity and mortality rates, reflect the strict protocols of care for pre-operative assessment, standardised intra-operative monitoring, minimal transfusion, peri-operative goal directed fluid management, early extubation with 24- to 36-hour stabilisation and epidural pain management for five postoperative days. The low morbidity and mean hospital stay of 10.5 days are among the lowest of other reported series[25,38,40,41]. The MDT selection process is focused on discriminating systemic versus peritoneal disease (median PCI of 7 in our series) and fitness for major surgery. However, it is possible that there is bias both in referral and selection that denies CRS/HIPEC treatment from a

subgroup of patients who could get some clinical benefit. This study confirms that CRS/HIPEC can be performed safely with minimal postoperative mortality and acceptable morbidity when performed in the setting of an experienced centre undertaking a high volume of cases.

The deficiency of this study includes the non-randomised case series, the retrospective nature, and the selection bias; however, this data provides accurate, real time information regarding outcomes for patients with CRPM. The median OS of patients selected for CRS/HIPEC was 46 months. Hence whilst potential curative cytoreduction can be achieved in some, benefits in survival can endure following CRS/ HIPEC even when complete CRS is not possible. Equally important is the data confirming median OS of 13.2 months for patients not offered CRS/HIPEC, which parallels the ARCAD[23] study and adds to our knowledge relating to current systemic anticancer treatment (SACT) for PM, an area that has been relatively neglected in the oncological literature. A recent editorial has commentated on the lack of inclusion of PM in trials of chemotherapy and inadequate data on outcomes of patients with PM as opposed to other metastatic sites from colorectal cancer[23]. The results of the PRODIGE 7 (P7) randomised trial of CRS alone versus CRS/HIPEC has yet to be published beyond abstract format but has been the subject of a commentary questioning the role of HIPEC [42,43]. Although the trialists must be commended on their work and efforts to evaluate the role of HIPEC, additional scrutiny of P7 has raised more questions. The unexpected benefit of CRS alone on median survival tests the validity of the number of patients in each arm, whilst the greater complication rate in the HIPEC arm (not seen in this series with a lower dose of oxaliplatin) may have influenced the median survival in that group. The authors have presented data (PSOGI Sept 2018 Paris) wherein for PCI < 15 there was a statistical difference in those receiving HIPEC. From the data available P7 demonstrates that CRS alone can be advantageous in CRPM whilst the additional role and appropriate dose of HIPEC requires further evaluation. Until so, this study provides valuable information for oncologists and patients regarding prognosis when peritoneal metastases are diagnosed and should encourage earlier referral and assessment regarding alternative treatments.

5. Conclusions

For CRPM patients who undergo CRS/HIPEC a low morbidity and mortality can be achieved and a survival benefit can be obtained. Increasing awareness of the potential benefits and low risks of CRS/HIPEC for CRPM should promote an increase in referrals. An experienced MDT should mentor new providers reducing the learning curve for selecting patients for potentially curative treatment of PM of colorectal origin.

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Tables

Table 1: Criteria for commissioning patients, according to NHS England[3]

Table 1
Patients must meet the following criteria:
Peritoneal neoplasms (benign and malignant) of appendiceal or colorectal origin
Disease distribution amenable to complete or near complete (residual individual tumours being no bigger than 2.5mm diameter – CC0 or CC1) surgical resection
Absence of systemic disease at the time of referral i.e. could have been Dukes C treatment with adjuvant chemotherapy at initial presentation (nodal positivity, unresectable distant metastases)
Performance status sufficient to withstand a major surgical procedure
Availability of all previous relevant imaging, histology and medical notes
Exclusion Criteria:
Unresectable disease (>CC2)
Significant co-morbidities
Peritoneal carcinomatosis* of non-colorectal origin

*Carcinomatosis is the term used by NHS England Commissioning although the preferred terminology is peritoneal metastasis

Table 2: Published studies showing the survival advantage of CRS and HIPEC

Table 2						
1st Author	**Year**	**Study design**	**N**	**Key Findings (median OS in months)**		
				CRS + HIPEC offered	**CRS + HIPEC not offered**	**p value**
Verwaal et al.[2]	2003	RCT	105	**22.3**	**12.6**	**.032**
Glehen et al.[20] *	2004	Retrospective	506	**32.4**	**8.4**	**<.001**
Elias et al.[18]	2009	Retrospective	96	**62.7**	**23.9**	**<.05**
Elias et al.[21] *	2010	Retrospective	523	**33**	**7**	**<.0001**
Cashin et al.	2016	RCT	48	**25**	**18**	**.04**
Larentzakis et al.	2017	Prospective register	286	**46**	**13**	**N/A**

* EPIC was also used in a group of patients

CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, N: number of study sample, OS: overall survival, RCT: randomized controlled trial, N/A: not applicable

Figure legends

Figure 1.

Temporal distribution of CRPM referrals per year. The study evaluated referrals from January 2002 to June 2015 (*2015 half year only).

Figure 2.

CRS/HIPEC has not been offered, according to MDT recommendations. Percentages correspond to the 117 of 286 patients not receiving treatment.

Figure 3.

Temporal distribution of CRPM referrals per referral period, and the declining percentage of patients over the three referral periods.

Figure 4.

Overall survival of i) patients that received CRS/HIPEC (survival data were available for 114 of the 117 patients), ii) patients that did not receive CRS/HIPEC at the Christie. iii) Overall survival from chemotherapy trials only, from the ARCAD consortium included for descriptive comparison[23]. No statistical testing performed as the treatment groups are no directly comparable. Time in months.

Figure 1

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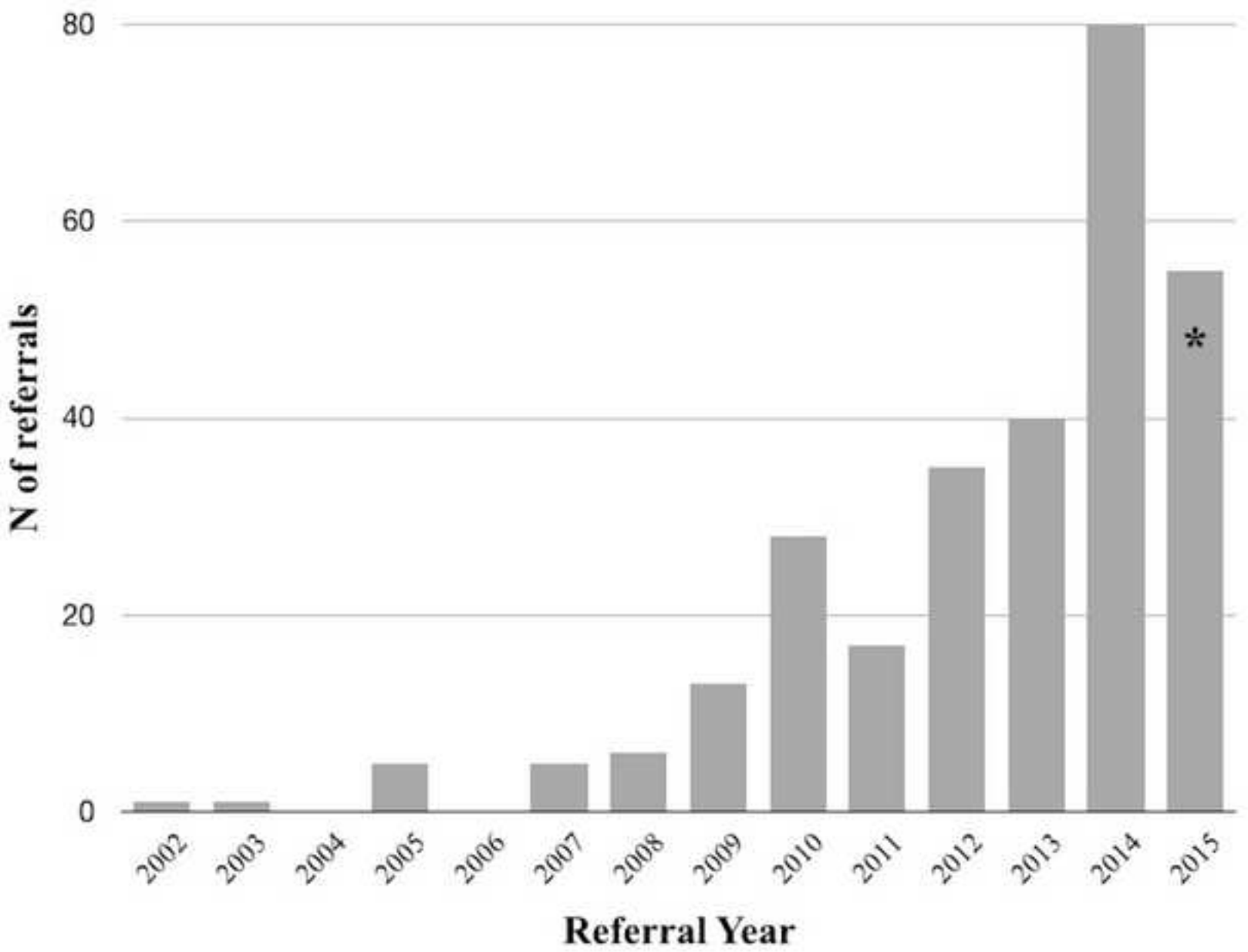

Figure 2

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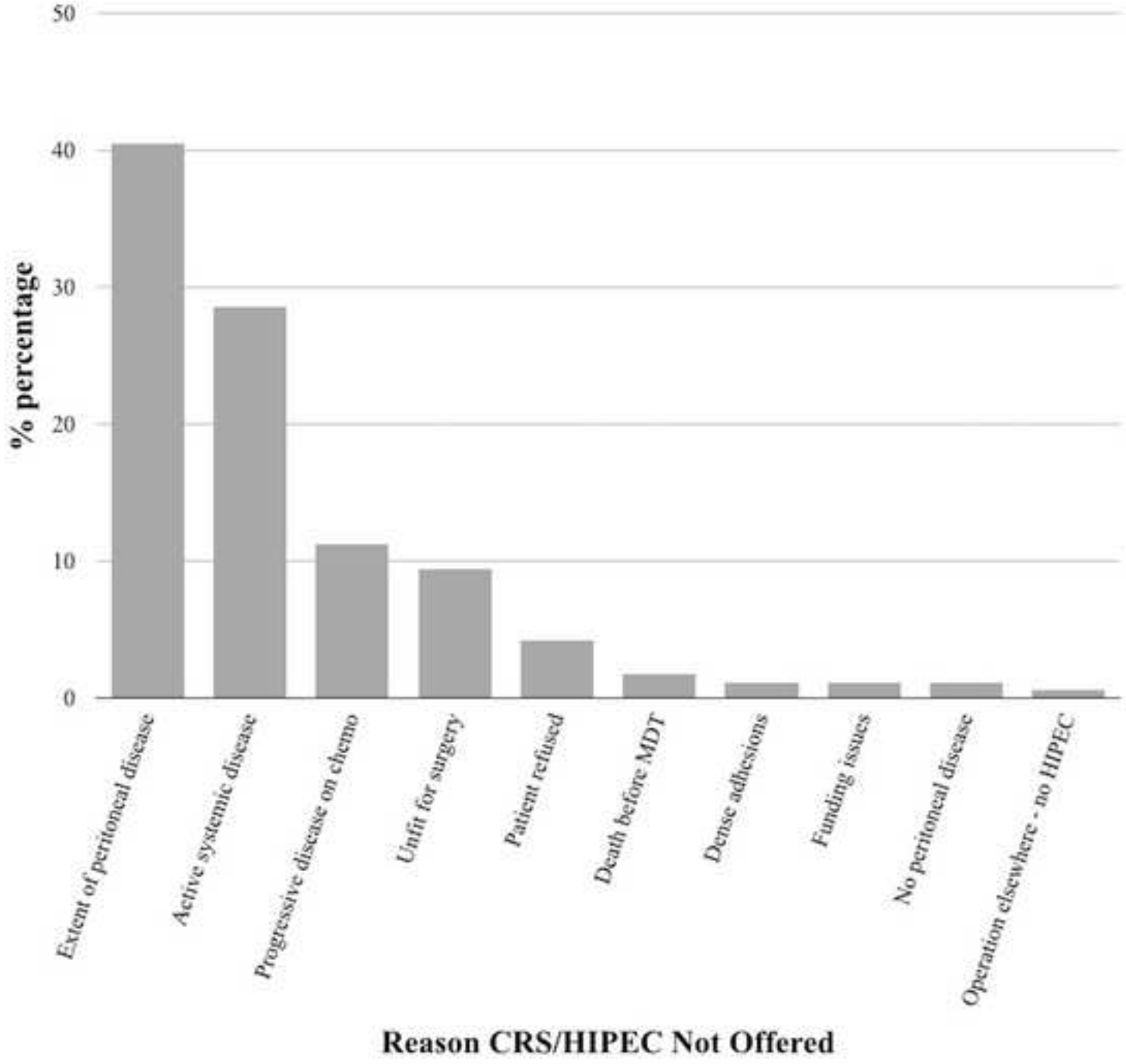

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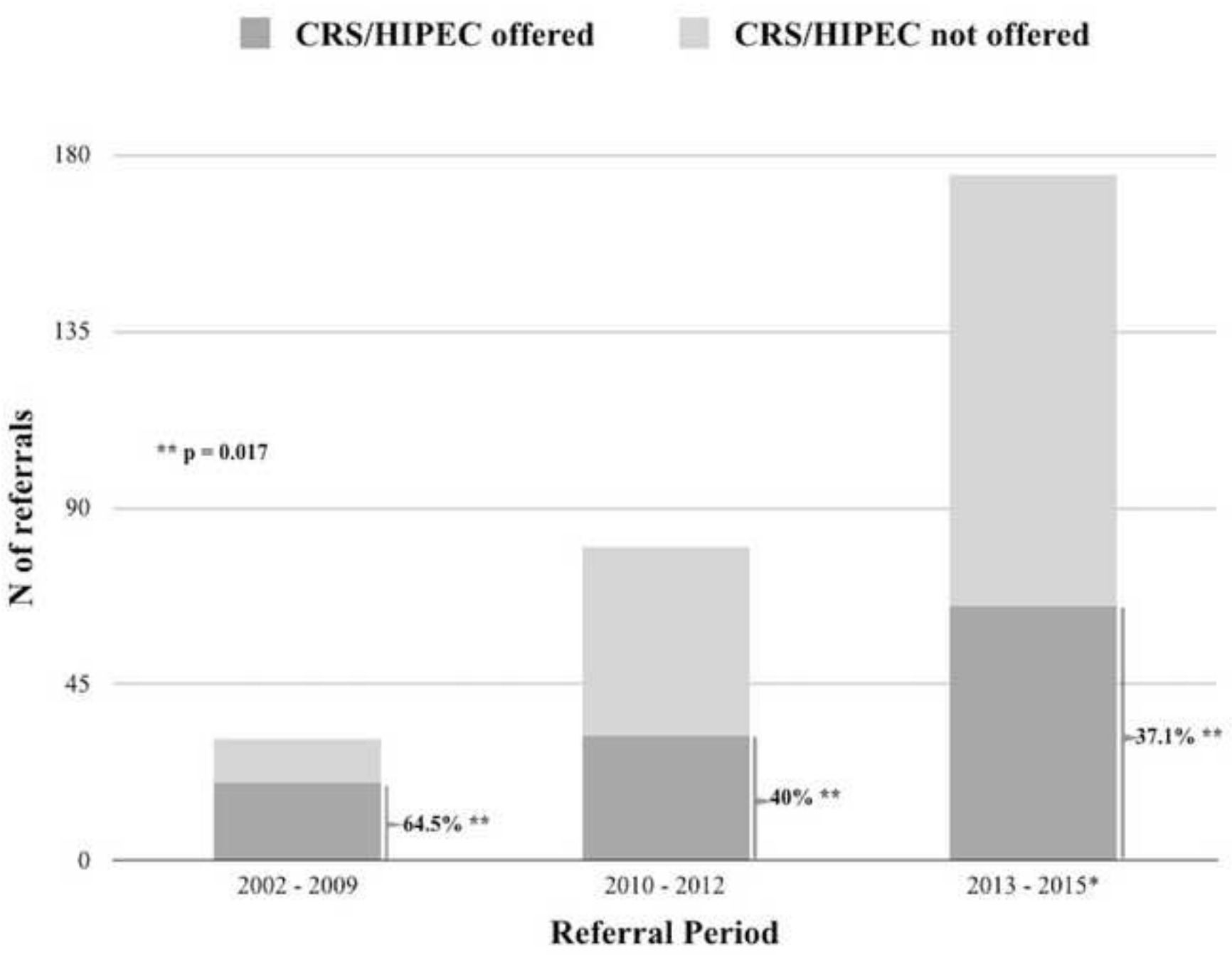

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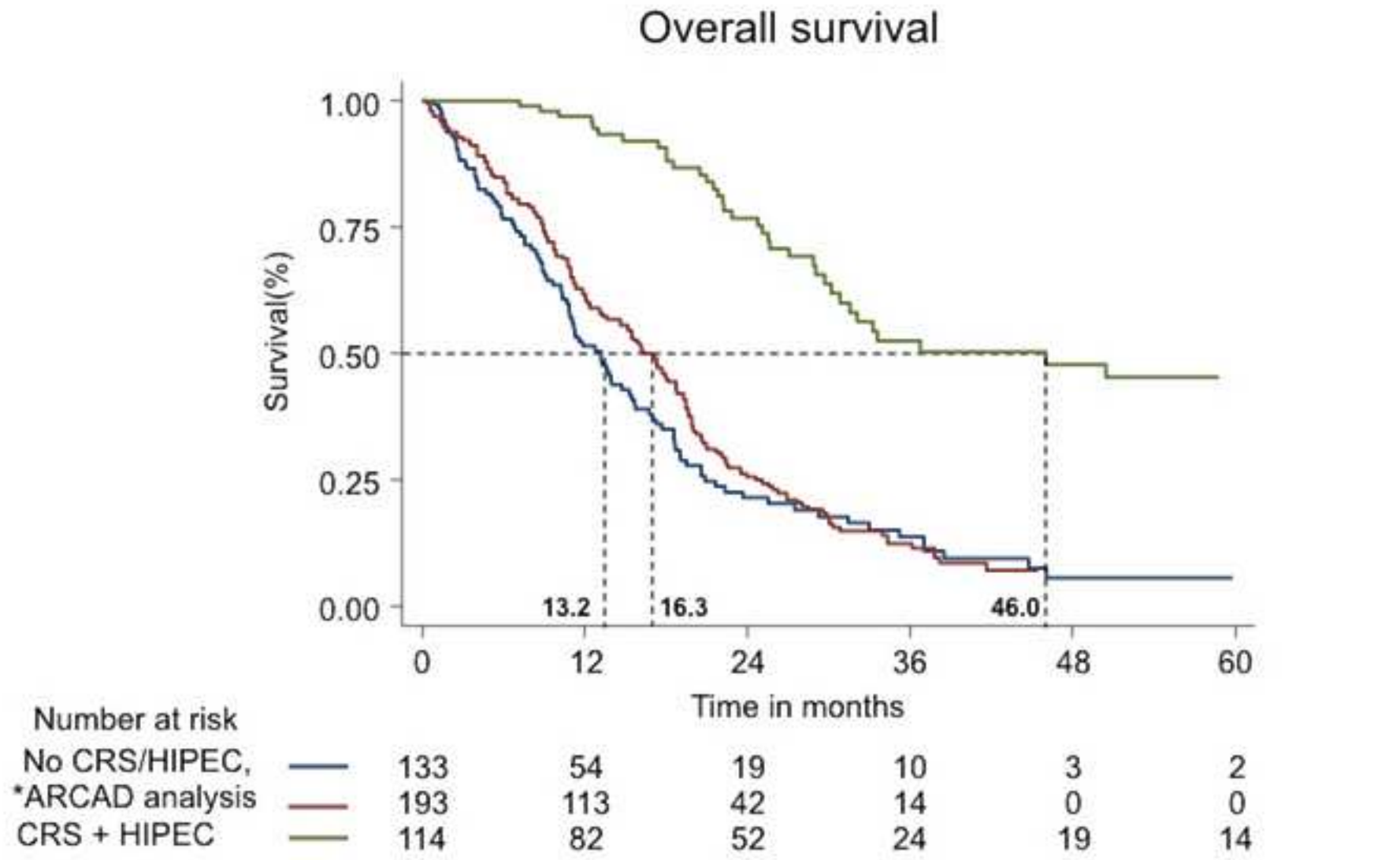

*Franko et al. Lancet Oncology 2016