Helsedirektoratet

Helhetlig gjennomgang av nasjonale og flerregionale behandlingstjenester i spesialisthelsetjenesten 2017

Spørsmål til lederen av behandlingstjenesten

SETT MARKØREN I DET GRÅ FELTET FØR DU STARTER SKRIVINGEN.

Navn på tjenesten:	Nasjonal behandlingstjeneste for hyperterm intraperitoneal kjemoterapi (HIPEC) ved kolorektal kreft, psudomyksoma peritoneii og peritonealt mesoteliom
Lokalisering:	Seksjon for onkologisk bekkenkirurgi Radiumhospitalet, Avd. for gastro- og barnekirurgi, OUS, Kreft-, kirurgi- og transplantasjonsklinikken, Oslo Universitetssykehus HF.

Tjenestens innhold

1. Det forutsettes at alle nasjonale og flerregionale behandlingstjenester har utarbeidet egne henvisningskriterier.

   Det bes om at tjenestens henvisningskriterier legges ved spørreskjemaet.

2. Gi en kort beskrivelse av insidens for de diagnosene som inngår i tjenestens ansvarsområde. (Med insidens menes i denne sammenheng antall genuint nye pasienter som er behandlet ved den nasjonale tjenesten i et aktuelt kalenderår. Hver pasient skal telles bare en gang i livet.)

Tjenesten tilbyr høyspesialisert kirurgi til pasienter i Norge ved 3 sykdommer: 1) colorectal kreft (begrensede peritoneale metastaser); 2) pseudomyxoma peritonei; og 3) abdominalt mesoteliom (begrensede peritoneale metastaser). Diagnostikk foregår ved henvisende sykehus, mens behandlingen, kombinasjonen av maksimal cytoreduktiv kirurgi (CRS; fjerning av all synlig tumor i buk/bukhinne) og deretter intraoperativ varm cellegiftbehandling i buken (HIPEC) foregår i behandlingstjenesten. Pasientene genereres blant nydiagnostiserte i Norge med pseudomyxom

(20-30 årlig), abdominalt mesoteliom (ca. 10), synkron carcinomatose fra colorectal cancer (ca. 80-100) og metakron carcinomatose (ca.100). Incidens for pseudomyxom er dermed ca 0,5/100000/ år. For abdominalt mesoteliom ca. 0,1/ 100000/ år. Incidensen for peritoneal carcinomatose fra colorectal cancer er vanskelig å anngi eksakt. I en stor studie fra Eindhoven cancer registry (Lemmens V 2010) er den angitt til 4,8% av antall colorectal cancere årlig. 2,7% har samtidige metastaser i lever eller lunge slik at 2,1% har peritoneale metastaser som eneste lokalisasjon. Overført til Norge blir incidensen av synkron carcinomatose da 1,7/100000/ år i Norge (4268 nye krefttilfeller 2015/5,2 mill innbyggere). I tillegg regner vi med at noen flere utvikler peritoneale metstaser seinere i kreftforløpet (tilsvarende antall). Behandlingen tilbys de som tilfredsstiller inklusjonskriteriene slik disse framkommer i helsedirektoratets nasjonale retningslinjer for colorectal kreft (vedlagt). Dette er pasienter < 75 år med begrenset sykdomsutbredelse og akseptabel komorbiditet.

Antall pasienter henholdsvis vurdert og akseptert i behandlingstjenesten samt gitt CRS-HIPEC gjenspeiler befolkningsfordelingen i landet. Flere pasienter fra hver av de 4 helseregioner har fått HIPEC i 2016 enn året før, men økningen har vært større fra Helse Midt og Helse Nord enn fra Vest og Sør-Øst. Antall HIPEC behandlinger er økt fra 58 til hele 83 dette året (+ 43 %). Fordelt på helseregioner er tallene for vurderte /opererte og gitt HIPEC slik: Helse Sør-Øst 168 (64,1 %), 74 (66,7%) og 55 (66,3%); Helse Midt-Norge 28 (10,7%), 10 (9,0%) og 9 (10,8%); Helse Nord 23 (8,8%), 10 (9,0%) og 7 (8,4%); Helse Vest 42 (16,0%), 14 (14,6%) og 9 (15,5%). 1 pasient med omfattende sykdom er behandlet for Sverige (0,4 %) da de i juli hadde for liten behandlingskapasitet. Rekordmange er vurdert i tjenesten i år, 261 pasienter (økning 5,7 %), hvorav 30 har flere vurderinger i løpet av året.

Den høyspesialiserte og svært tidkrevende kirurgien, median >8 timer operasjon, utføres på Radiumhospitalet. Alle pasienter vurderes innen 1 uke(MDT) og pasienter mottas til kirurgi i løpet av kort tid. Selve HIPEC forlenger operasjonstiden med 3 timer. Varm cellegift(42°C) sirkulerer i bukhulen i 90 minutter. Cellegiftbehandlingen gis i et lukket system. Det brukes hovedsakelig Mitomycin C(max 70 mg), ved abdominalt mesoteliom Cisplatin/Doxorubicin, og en oppnår høye konsentrasjoner i bukhulen med begrenset systemisk toksisitet. Pasientene tilbys dedikert kirurgi, god informasjon og god sykepleie. De fleste utskrives til hjemmet etter 9 dager(median). Første kreftkontroll er i behandlingstjenesten etter 3 mnd. Deretter foregår oppfølging i egen helseregion. En prospektive MedInSight peritoneal kreft database inkluderer og overvåker alle pasienter (1300 inkluderte pasienter). Pas. får informasjon om vurderingen i den nasjonale behandlingstjenesten av henvisende sykehus, men tilbys samtale hos oss ved behov.

Ved påvisning av peritoneale metastaser under primæroperasjon av tykk- og endetarmskreft på egne lokale sykehus anbefales at primærtumor fjernes, men at det gjøres minst mulig kirurgi på den peritoneale sykdommensutbredelen. Omfattende tidligere kirurgi vanskeliggjør CRS-HIPEC. Behandlingsresultatene er også bedre om pasienten henvises når peritoneale metastaser påvises, enn seinere. Pasienter som har sentrale glandelmetastaser, ikke-resektable organmetastaser eller generell carcinomatose på større avsnitt av tynntarmen egner seg ikke til slik behandling og ekskluderes. Det samme gjelder stor overflateutbredelse av sykdom (Peritoneal Cancer Index(PCI) over 22-25. Alternativ behandling er palliativ cellegiftbehandling.

3. Har tjenestens innhold (behandlingsmetode og/eller volum) og avgrensninger mot andre

deler av helsetjenesten endret seg de siste 5 år?

Volumet var stabilt i perioden 2012-15, men økt en del i 2016 (se under p.2). Behandlingsmetode har vært uforandret over noen år mens noen fler en tidligere med synkrone peritoneale metastaser har fått behandling i 2016.

4. Finnes det andre behandlingsmetoder for de diagnoser/skader som inngår i tjenestens ansvarsområde?

Nei. Andelen av opererte uten at HIPEC kan gis er også gått ved fra 40 % til 25 % siste året. Pasienter som har sentrale glandelmetastaser, ikke-resektable organmetastaser eller generell carcinomatose på større avsnitt av tynntarmen egner seg ikke til slik behandling og ekskluderes hvis dette er kjent. Dette skjer i tverrfaglige møter 1-2 ganger hver uke i behandlingstjenesten. Ved stor overflateutbredelse av sykdom ved peritoneale metastaser (Peritoneal Cancer Index(PCI) over 22-25 er kirurgien heller ikke mulig. Pseudomyksom kan behandles ved langt høyere index. Alternativ behandling er palliativ cellegiftbehandling ved onkologisk enhet på hjemstedet.

5. Hva er hovedbegrunnelsen for at denne tjenesten fortsatt skal være sentralisert?

CRS-HIPEC er en svært spesiell og ressurskrevende prosedyre på en kompleks og liten pasientgruppe. Driften er høyspesialisert, lærekurven lang og det er gode publikasjoner på resultat knyttet til volum betraktninger og lærekurve over mange år. I ledende land i feltet arbeider en mot 1 senter pr. 5-10 million innbyggere som et optimalt nedslagsområde.

I Norge er vi et av 6-8 land som har nasjonale retningslinjer for behandlingen gitt av Helsedirektoratet.

Norge er et lite land med kun 5.2 mill. innbyggere og vår vurdering er at 1 behandlingssenter for CRS-HIPEC fortsatt er tilstrekkelig for å dekke det nasjonale behovet. Tjenesten er robust, og 6-8 spesialister deltar i kirurgien. Det er utviklet gode beredskapsplaner og sikringer av nødvendig kvalitet og tilgang for korte ventetider til vurdering og behandling. Kapasiteten økes i perioder med større pågang for å sikre pasienter behandling på kort varsel.

Bemanning

6. For å sikre kontinuitet er det forutsatt at det skal være ansatt minst tre fagpersoner pr. fagspesialitet som kan ivareta behandlingstilbudet i en nasjonal behandlingstjeneste. Gi en kort redegjørelse for hvordan dette kravet er oppfylt for denne tjenesten.

3 av seksjonens gastrokirurger (overleger) er hovedansvarlige og våre retningslinjer er at en av disse skal være tilgjengelig. Også de 6 andre gastrokirurgene i seksjonen kan utføre hele/ eller mesteparten av kirurgien og disse og de 2 faste underordnede legene (spesialiseter i 2017) bidrar med delprosedyrer under den lange og krevende kirurgien. Virksomheten har tilknyttet dedikerte onkologer fra kreftklinikken og dedikerte radiologer fra billedklinikken.

Kvalitet

7. Nasjonale tjenester skal bidra til økt kvalitet på utredning og behandling av en definert og

avgrenset pasientgruppe. Det bes om dokumentasjon på oppnådde behandlingsresultater og andre kvalitetsmål som tjenesten har etablert.

Behandlingstjenesten har erfaring med operasjonsteknikken med peritonectomi helt fra 1994 og teknikk justeres løpende. Det har vært 3 større endringer i perioden; a) 5-døgns intraabdominell cellegiftbehandling (EPIC)1994-2003; b) åpen peroperativ cellegiftkjøring etter kirurgi (2003-8); c)dagens lukkede HIPEC teknikk fra 2008. Lærekurven knyttet til kompleks kirurgi er gjennom et 500-talls prosedyrer ivaretatt, og kort- og langtidsresultater er sammenliknbare med ledende sentra internasjonalt.

Gode kontrolldata er viktig for å overvåke behandlingsmetoder, behandlingsresultater, og for å oppdage evt. sykdomsprogresjon og kanalisere pasientene til adekvat oppfølging og behandling i pasientens egen helseregion. Vi har meget gode system for overvåkning av behandlingsresultater da alle data om henvisningspraksis fra samarbeidende sykehus, fylker og helseregioner registreres i vår MedInSight forskningsdatabase som nå inneholder data om 1300 pasienter. Vi følger viktige parametre for å vurdere egen tjeneste som f.eks: Helseregionsfordeling; tid til vurdering og behandling; epikrisetid; andel eksplorative inngrep i forhold til opererte i behandlingstjenesten; komplikasjoner: 100 dagers dødelighet; 5-års overlevelse; tumorutbredelse og ressursbruk.

I årsrapporten for 2016 valgte vi i å fokusere på pasientdata publisert i vår hovedartikkel (EJSO2016, vedlagt) som viser behandlingsresultater lang over vanlig systemisk kjemoterapi med 5-års overlevelse 36 %, median 47 mnd, uten noen 100-dagers dødelighet. Det omhandler 119 pasienter opererte med PC fra colorectal cancer (origo utenom blindtarmen) operert fra januar 2004 – desember 2013. 15 % hadde komplikasjoner som trengte innleggelse av dren eller reoperasjon for (Accordion ≥3), PCI index 9 (0-18). En del utvikler recidiv sykdom i bukhule, andre fjernmetastaser og noen blir sensorert pga kort oppfølging før lukking av studien, slik at 5-års sykdomsfri overlevelse blir lav (14 %). Dette er også i nivå med hva andre ledende senra har publisert. Behandlingsalternativet er omfattende systemisk behandling med forventet median overlevelse ca 2 år. Vi har fortsatt median liggetid på 9 dager (PC) og 11 dager (pseudomyxom) som er lave. Reoperasjonsraten er lav på 15 % (som ledende sentra), og vi har fortsatt 0 % mortalitet etter 100 dager i PC gruppen og lav mortalitet også ved behandling av pseudomyxom.

Antall radikalopererte uten HIPEC var 7 i 2016, antall palliativ opererte 8, og antall med kun eksplorativ laparotomi 13 (11,7 %). Raten for eksplorerte er en av mange kvalitetsmål vi årlig vurderer. 11,7% er i det nivået vi ønsker, da vi selvfølgelig vil unngå at pasienter som kunne ha nytte av behandlingen ikke får tilbudet, og dermed ønsker heller at vi eksplorerer noen få unødvendig.

Kompetansespredning

8. En nasjonal eller flerregional behandlingstjeneste skal blant annet spre informasjon om tjenestens innhold, behandlingstilbud, henvisningskriterier, henvisningsrutiner og understøttelse av at helhetlig pasientforløp til helsepersonell og brukere av tjenesten. Det forventes derfor at alle nasjonale tjenester har utarbeidet en plan for kompetansespredning.

Det bes om at plan for kompetansespredning legges ved.

Tilleggsinformasjon

9. Eventuelle andre forhold som er viktig for å forstå hvordan tjenesten fungerer som en nasjonal eller flerregional behandlingstjeneste:

Nytt nå i 2016/17 er at vi arbeider med et fellesprosjekt i alle helseregioner der vi ser på ulike faktorers betydning for om pasienter kan opereres, og for om vi kan kalkulere sjanse for operabilitet eller forusi prognosen bedre enn i dag. Vi synes det er viktig å få til fellesprosjekter der alle helseregioner kan bidra. En kan også tenke seg en "Norwegian HIPEC study group" med ulike bidrag.

De nasjonale retningslinjene er publisert på hjemmesiden:

https://oslo-universitetssykehus.no/behandlinger/crshipec-behandling,

på www.oncolex.no

http://oncolex.no/Peritoneum

og i handlingsplan for colorectal cancer, side 74-77:
http://ngicg.no/handlingsprogram/nasjonale_handlingsprogrammer/

Signering av ansvarlig leder

Dato og underskrift:

25.02.17 Stein Gunnar Larsen,

Leder av behandlingstjenesten, seksjonsoverlege gastrokiriurgi.

Vedlegg

Det bes om følgende vedlegg:

- Tjenestens plan for kompetansespredning
- Henvisningskriterier til tjenesten
- Dokumentasjon for oppnådde behandlingsresultater og kvalitetsmål

191216 arl

Plan for kompetansespredning:

Nasjonal behandlingstjeneste for hyperterm intraperitoneal kjemoterapi (HIPEC) ved kolorektal kreft, psudomyksoma peritoneii og peritonealt mesoteliom.

Målet for kompetansespredningen er at kolleger som behandler pasienter med de 3 tilstandene henviser de riktige til kirurgisk behandling i behandlingstjenesten. Oppfølging skjer i eget distrikt.

Hovedelementet i planen er:

- ha årlige innlegg på kirurgisk høstmøte og publisere i internasjonale tidsskrift,

- holde foredrag i ulike fagmiljøer jevnlig

- ta imot kolleger som ønsker å hospitere hos oss slik at de kan delta ved operasjon og tverrfaglige møter.

- Holde foredrag i ulike pasientfora.

-Følge opp kolleger på kirurgiske-/ gynekologiske- og onkologiske avd.

Gjennomførte tiltak 2016:

Enheten har bygget opp en økende forskningsaktivitet og det er startet et fellesprosjekt som involverer alle helseregioner, startet arbeid med en nordisk samarbeidsorganisasjon og fortsatt kontakt med noen europeiske sentra (se under prosjekter). Det er etablert god kontakt mot forskningsinstituttet, både i dyreeksperimentelle studier, i basalforskning og i klinisk forskning. Alle henviste pasienter inkluderes løpende i forskningsdatabasen MedInSight peritoneal cancer som inneholder opplysninger om alle opererte pasienter fra starten i 1994, og om alle henviste fra mai 2010. Egne resultater overvåkes kontinuerlig. Den prospektive basen utvikles stadig. Det tas tumor- og blodprøver til egen biobank av alle som samtykker og basen inneholder blodprøver og overskuddsvev systematisk samling fra høsten 2013, og 100 før dette mer usystematisk. To PhD prosjekter er pågående; 1 har vært forsinket men innleveres våren 2017 (eksperimentell HIPEC; Olaf Sørensen, 3 art publisert) og et er godt i gjenge (ImmunoPeCa- Immuntoksinbehandling ved spredning til bukhinnen fra kolorektal kreft; Ida Frøysnes, 2 art. publisert).

Vår seksjon har i 2014/15 tatt initiativ til et europeisk multisenter samarbeid rundt pseudomyxoma peritoneii (Cure4PMP; partnere fra Storbritannia (Manchester, Basingstoke/Southampton), Belgia (Genk) og Frankrike (Lyon, Paris)). En søknad om EU-midler nådde ikke fram i denne runden, men vi ble støttet med midler fra National Organisation for Rare Diseases, (NORD), USA med prosjektstart i 2016. PMP har vært et sentralt fokusområde i vår avd på Radiumhospitalet siden 1994.

Behandlingstjenesten hadde i 2016 flere norske gastrokirurger på gjesteopphold. Vi bidrar med innspill om behandlingen i en rekke faglige møter og jobber for at alle deler av den spesialiserte kreftomsorgen kjenner tilbudet vårt slik at pasienter som omfattes av tilbudet henvises uansett hvor de bor og hvilket sykehus de tilhører. Enheten praktiserer lik tilgang til tjenesten for pasienter fra alle helseregioner. En klinisk fase I studie, med MOC31PE immuntoksin (startet 2014) ble fullført i 2016 og manuskript er akseptert i Annals of Surgical Oncology. Egen internettside for behandlingstjenesten fra 2015 utvikles, flow-skjemaer for å lette seleksjonen

Nasjonale faglige retningslinjer
IS-2283

Helsedirektoratet

Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm

Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Peritoneal Metastasis in Norway: Prognostic Factors and Oncologic Outcome in a National Patient Cohort

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Background and Objectives: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) can offer long-term survival to patients with resectable peritoneal metastasis (PM) from colorectal cancer (CRC), a condition with otherwise dismal prognosis. This study describes short- and long-term outcome in a national patient cohort and aims to identify prognostic factors.
Methods: All patients treated with CRS-HIPEC for non-appendiceal PM-CRC in Norway 2004–2013 were included (n = 119), and outcome and potential prognostic factors were examined using survival- and ROC-curve analysis.
Results: Five-year overall survival (OS) and disease-free survival (DFS) were 36% and 14%, respectively, with 45 months median follow-up. The only factor associated with OS in multivariable analysis was peritoneal cancer index (PCI), with HR 1.05 (1.01–1.09) for every increase in PCI-score ($P = 0.015$). Peritoneal relapse was associated with shorter OS than distant metastasis ($P = 0.002$). ROC-curves identified PCI > 12 as a marker with 100% specificity for prediction of disease relapse. Severe postoperative complications (Clavien–Dindo ≥ 3) occurred in 15% of patients and there was no 100-day mortality.
Conclusions: Long-term outcome was in line with published results, morbidity was acceptable and there was no 100-day mortality. The results reemphasize CRS-HIPEC as an important treatment option in PM-CRC, with particularly good results in patients with PCI < 12.
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KEY WORDS: **colorectal cancer; peritoneal metastasis; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy**

INTRODUCTION

Peritoneal metastasis (PM) from colorectal cancer (CRC) is a condition with poor prognosis, historically with median overall survival (OS) of less than 7 months [1–3]. The introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has given patients with limited and resectable disease in the peritoneal cavity a possibility of long-term survival and even cure, as shown in one randomized controlled trial comparing CRS-HIPEC to palliative systemic chemotherapy with 5-fluorouracil [4], a limited number of case-control studies [5–7] and several cohort studies [8]. However, in the absence of randomized controlled trials comparing CRS to CRS-HIPEC, it is unclear whether the apparent prolonged survival is caused by the combination of CRS-HIPEC and not CRS alone, and if selection bias may have influenced the choice between surgery versus palliative chemotherapy. A main challenge in the field of CRS-HIPEC is furthermore patient selection, as the procedure is associated with mortality and morbidity, as well as considerable variation in long-term outcome.

The Norwegian Radium Hospital, now part of Oslo University Hospital, has as the only centre in Norway performed CRS combined with intraperitoneal chemotherapy since 1994, initially treating pseudomyxoma peritonei [9], but from 2004 also PM-CRC. Today, the Norwegian National Unit for Hyperthermic Intraperitoneal Chemotherapy in Colorectal Cancer, Pseudomyxoma Peritonei and Abdominal Mesothelioma serves the entire Norwegian population of more than five million. National treatment guidelines, which are based on recommendations from the Norwegian Directorate of Health through the Norwegian Gastro Intestinal Cancer Group, were implemented in 2009 and secure equal treatment regardless of geographical location and socio-economic status. The aim of this study was to investigate short- and long-term outcome in all patients treated with CRS-HIPEC for PM-CRC in Norway from 2004 through 2013, and to identify factors associated with disease outcome.

PATIENTS AND METHODS

Patient Population

Between January 2004 and December 2013, 229 patients underwent surgery for suspected or verified PM from CRC or appendiceal cancer at the Norwegian Radium Hospital. Eighty-five of these patients did not receive HIPEC for the following reasons: unresectable disease (n = 59), organ- or lymph-node metastasis (n = 9), PM not verified (n = 3), or

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Ida S. Frøysnes and Stein G. Larsen contributed equally to this work.

Conflict of interest: None.

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Helsedirektoratet God helse - gode liv

National guidelines
Inclusion criteria in colorectal cancer

1. Limited peritoneal carcinomatosis in synchronous or metachronous colorectal cancer, without systemic disease

2. Second look 6-12 mnd after presumed curative primary operation (and systemic chemo) for colorectal cancer in asymphtomatic patients with high risk for developing carcinomatose:

   - metastases to ovaries

   - one or few tumour nodules in peritoneum earlier removed

   - tumour perforation

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www.ejso.com

Evaluation of complete cytoreductive surgery and two intraperitoneal chemotherapy techniques in pseudomyxoma peritonei

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Abstract

Background: Pseudomyxoma peritonei (PMP) is a low-grade malignancy characterized by mucinous tumor on the peritoneal surface. Treatment involves cytoreductive surgery (CRS) to remove all macroscopic tumor and perioperative intraperitoneal chemotherapy (PIC) to eliminate remaining microscopic disease.
Patients and methods: Between 1994 and 2009, 93 patients were treated at the Norwegian Radium Hospital with complete CRS and PIC. PIC was administered as early postoperative intraperitoneal chemotherapy (EPIC) using mitomycin C (MMC) and 5-fluoruracil ($n = 48$) and as hyperthermic intraperitoneal chemotherapy (HIPEC) using MMC ($n = 45$). Patients were classified into three histopathological subgroups: Disseminated peritoneal adenomucinosis ($n = 57$), peritoneal mucinous carcinomatosis ($n = 21$) and an intermediate group ($n = 15$). Tumor distribution by peritoneal cancer index (PCI) was PCI $\leq$10 ($n = 31$), PCI 11–20 ($n = 29$), PCI $\geq$21 ($n = 33$).
Results: Recurrence was diagnosed in 38 patients and 25 patients died during follow-up. Estimated 10-year overall survival (OS) was 69% and 10-year disease-free survival (DFS) was 47%. Mean OS was 154 months (95% CI 131–171) and median OS was not reached (follow-up median 85 months (3–207)). Low-grade malignant histology ($p = 0.001$) and female gender ($p = 0.045$) were associated with improved OS. Almost equal OS and DFS were observed between patients treated with EPIC and HIPEC.
Conclusions: Patients treated for PMP with complete CRS and PIC achieved satisfactory long-term outcome. The most important prognostic factor was histopathological differentiation, but acceptable survival was observed even in patients with aggressive histology and extensive intraperitoneal tumor growth. Administration of EPIC and HIPEC was equally efficacious with respect to long-term outcome.
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Keywords: Pseudomyxoma peritonei; Cytoreductive surgery; EPIC; HIPEC; Mitomycin C

Introduction

Pseudomyxoma peritonei (PMP) is a rare, low-grade malignancy that usually originates from a ruptured mucinous neoplasm of the appendix. While metastasis by the lymphatic and hematogenous routes rarely occurs, tumor cells are released directly into the peritoneal cavity and distributed throughout this compartment by the peritoneal fluid. Because of a modest tendency for tissue adhesion and invasion, the cells are entrapped on the peritoneal surface mainly at locations defined by fluid absorption (greater omentum, right diaphragm) and gravity (pelvic cavity,

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paracolic gutters). In contrast, the small bowel is protected from tumor deposition by peristaltic movements and in most cases only sparsely affected by the disease.[1] Because the peritoneum is a barrier that protects the neighboring structures from invasive tumor growth, PMP is usually limited to the peritoneal cavity.[2]

The natural course of PMP typically involves slow disease progression until death caused by complications of massive tumor growth and high intra abdominal pressure. Previously, debulking surgery was the only available treatment option.[3,4] High recurrence rate and increasingly invasive tumor growth at each intervention finally made further treatment impossible. In the 1980s, a multimodal and potentially curative treatment strategy was introduced.[5] By combining cytoreductive surgery (CRS) to remove macroscopic tumor and perioperative intraperitoneal chemotherapy (PIC) for elimination of microscopic residual disease, 10-year survival increased from previously observed 20–30% up to more than 70%.[6,7] Furthermore, PMP has gained importance as a "model disease" for peritoneal surface malignancies and the treatment strategy developed for this disease is increasingly being administered to patients with peritoneal carcinomatosis from more aggressive malignancies.

The Norwegian Radium Hospital has since 1994, as the only institution in Norway, offered CRS and PIC for patients with PMP. This study reviews our experience from the first 15 years and tries to identify clinicopathological factors of prognostic importance, with a particular focus on histopathological subtypes and intraoperative versus early postoperative intraperitoneal chemotherapy.

Patients and methods

Patients

In the period between September 1994 and December 2009, 120 consecutive patients diagnosed with PMP were accepted for treatment with CRS and PIC. In 27 patients, the complete procedure was for the following reasons not performed: Too extensive tumor growth, rendering CRS impossible ($n = 16$); severe per-operative complications, including three cases of fatal bleeding ($n = 5$); no residual tumor after previous surgery in referring hospital ($n = 2$); palliative resection and PIC ($n = 2$); mucocele appendix without perforation ($n = 1$) and lymph node metastasis detected per-operatively ($n = 1$). In 93 patients, hereafter referred to as the study group, CRS and PIC were performed. The median age was 55 years (24–76), 67 females and 26 males. Between 1994 and 2002, PIC was administered as early postoperative intraperitoneal chemotherapy (EPIC, $n = 48$), from 2003 onward as hyperthermic intraperitoneal chemotherapy (HIPEC, $n = 45$). The study was approved by the Regional Ethics Committee, and patient informed consent was obtained in accordance with the Helsinki Declaration. Data regarding patients, disease and treatment were partly prospectively registered into the institutional peritoneal surface malignancy database, partly retrospectively obtained from the patient charts. Preoperative work-up was based on operative reports from referring hospital, thoraco–abdominal–pelvic CT scan (alternatively chest X-ray for lung examination). The extent of previous tumor resection was assessed by the number of abdominal regions that had undergone surgical dissection and classified according to prior surgery score (PSS): PSS-0, no surgery, biopsy or laparoscopy; PSS-1, one region; PSS-2, 2–5 regions and PSS-3, 6–9 regions.[8]

Assessment of peritoneal tumor distribution

Tumor distribution on the peritoneal surface was classified according to peritoneal cancer index (PCI); before 2003 retrospectively estimated from operative reports and CT scans, thereafter prospectively registered. Thirteen peritoneal regions were given a score from 0 to 3 based on tumor size: 0, no macroscopic tumor; 1, tumor <0.5 cm; 2, tumor between 0.5 cm and 5 cm and 3, tumor >5 cm or confluent tumors.[8] After being assigned a PCI score between 0 and 39, the patients were categorized into three groups according to PCI intervals: PCI $\leq$10, PCI 11–20 and PCI $\geq$21.[9] Many patients had undergone extensive surgery at referring hospitals and in these cases, PCI assessed at the time of CRS underestimated the extent of the disease. Therefore, a parameter PCI_{max} was defined to describe the maximum tumor distribution before treatment, calculated as a combination of scores from operative reports and CT scans at referring hospital and findings during surgery at our hospital.

Cytoreductive surgery

CRS was conducted with the intention to remove all tumor bearing peritoneum, if necessary by organ resections, and classified according to six peritonectomy procedures described by Sugarbaker[10]: Total anterior parietal peritonectomy, omentectomy with or without splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy with or without low anterior resection and cholecystectomy, lesser omentectomy with stripping of the omental bursa. Residual tumor after CRS was classified using the Completeness of Cytoreduction (CC) score[8]: CC-0, no residual tumor; CC-1, residual tumor < 0.25 cm; CC-2, tumor between 0.25 cm–2.5 cm and CC-3, tumor >2.5 cm. Complete cytoreduction was defined as CC-0 and CC-1.

Perioperative intraperitoneal chemotherapy

For administration of EPIC, four percutaneous peritoneal catheters were introduced, one in each abdominal quadrant. The drugs used for EPIC were mitomycin C (MMC) 10 mg/m^2 on day 1 and 5-fluoruracil (5-FU) 650 mg/m^2 on days 2–5. The drugs were diluted in

1000 ml dextrose and were contained intraperitoneally for 23 h. Evacuation of remaining drug was immediately followed by instillation of the next dose.

For administration of HIPEC, the open Coliseum-technique was used until 2008 when a semi-open technique was introduced.[11,12] The perfusion system consisted of a Medtronic Biomedicus Bio-Console 560, originally used for advanced non-pulsatile heart–lung bypass; an external drive 540T including a bioprobe Tx4 electromagnetic in-line flow meter (Medtronic Inc. Minneapolis, USA); an in-line temperature monitor unit (Biocontrole type CF Biocal cardiopulmonary bypass temperature controller); a heater/cooler unit, modified to warm up to 43.5 °C, (Stoeckert Instruments GmbH, Germany); a custom built tubing set (Medtronic Inc.), consisting of a venous reservoir to be used as a compliance reservoir, including a SciMed heat-exchanger. One inflow and two outflow catheters were used; the latter were connected to temperature probes and located between the liver and right diaphragm and in the pelvic cavity. The drug used for HIPEC was MMC (35 mg/m^2, maximum 70 mg), added to the carrier solution (saline 0.9%) in three fractions of 50% (0 min), 25% (30 min) and 25% (60 min).[13] HIPEC was performed for 90 min except for four patients where the procedure for technical reasons was terminated after 60 min. In 26 patients, CRS and HIPEC were performed on the same day while 19 patients received HIPEC as a separate procedure, in most cases on the day after CRS. For the individual procedure, the mean perfusion flow rate and temperature were calculated from four registrations (0, 30, 60 and 90 min). In 45 HIPEC procedures, the median flow rate was 2.5 l/min (0.7–4.5) and the median temperature was 40.5 °C (39.5–41.6).

Histopathological evaluation

All tissue samples from referring hospitals and our institution were examined by the study pathologist (W.R.) and classified into three histopathological subgroups according to the criteria described by Ronnett et al.[14]: Disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis with intermediate features (PMCA-I) and peritoneal mucinous carcinomatosis (PMCA).

Follow-up

The patients attended the outpatient clinic for up to ten years, the first five years every six months and thereafter in most cases once yearly. Follow-up included clinical examination, thoraco–abdominal–pelvic CT scans (alternatively chest X-rays for lung examination) and serum analyses of tumor markers (CEA, CA 19-9, CA 125). Recurrence was defined as detection of mucinous tumor in the peritoneal cavity by CT scan. Follow-up analysis was terminated on December 31 2011, at which time updated survival data were obtained from the National Registry of Norway.

Statistical analysis

Associations between clinicopathological parameters and histopathological subgroups and mode of PIC were analyzed using the Chi-Square test (Pearson's and linear-by-linear association as appropriate). Mann–Whitney test and Kruskal–Wallis test were used to test for differences between independent groups of quantitative variables. Curves of overall survival (OS) and disease-free survival (DFS) were calculated from the date of CRS and PIC with the Kaplan–Meier product-limit method, for OS until date of death and for DFS until date of recurrence or death. Uneventful postoperative courses were censored on December 31 2011(OS) and on date of last follow-up (DFS). Differences between groups were analyzed using the log rank test. p-Values <0.05 were considered significant. Factors significant in univariate analysis and mode of PIC were included in multivariate analysis which was conducted by the Cox proportional hazards regression model with backward, stepwise elimination of variables. Statistical analyses were performed using the Statistical Package for the Social Sciences® program, version 18.0 (SPSS GmBH, Chicago, Illinois, USA).

Results

Tumor distribution and treatment

Assessment of previous surgery showed PSS-0, $n = 14$; PSS-1, $n = 25$; PSS-2, $n = 46$; PSS-3, $n = 8$. Tumor distribution at the time of CRS was as follows: PCI $\leq$10, $n = 31$; PCI 11–20, $n = 29$; PCI $\geq$21, $n = 33$. Calculated maximum tumor distribution, including records describing previous surgery, was PCI_{max} $\leq$10, $n = 20$; PCI_{max} 11–20, $n = 25$; PCI_{max} $\geq$21, $n = 48$. Ovarian metastasis was histologically verified in 40 of 67 female patients (60%). The duration of surgery was median 378 min (75–1500), where 1500 min is an extreme outlier representing the combined time spent on two successive procedures performed within one week, the maximum duration of a single procedure was 860 min. The median number of days in hospital was 15 (6–161), in intensive care unit 1 (0–66), on respirator 0 (0–45) and with parenteral nutrition 5 (0–93).

Associations between histopathology- and PIC-groups and clinical parameters

Details of descriptive data, with the patients stratified according to histopathological differentiation and mode of PIC, are given in Table 1. Histopathological classification showed DPAM in 57 patients, PMCA-I in 15 patients and PMCA in 21 patients. Aggressive histology (PMCA-I and PMCA) was associated with extensive tumor distribution; PCI $\geq$21 was found in 13 of 57 (23%) patients with DPAM, in 9 of 15 (60%) with PMCA-I and in 11 of 21 (52%) with PMCA. Accordingly, the PMCA-I and PMCA

Table 1
Patient characteristics for the study group, stratified according to perioperative intraperitoneal chemotherapy and histopathological differentiation. When appropriate, the numbers are given as median (range).

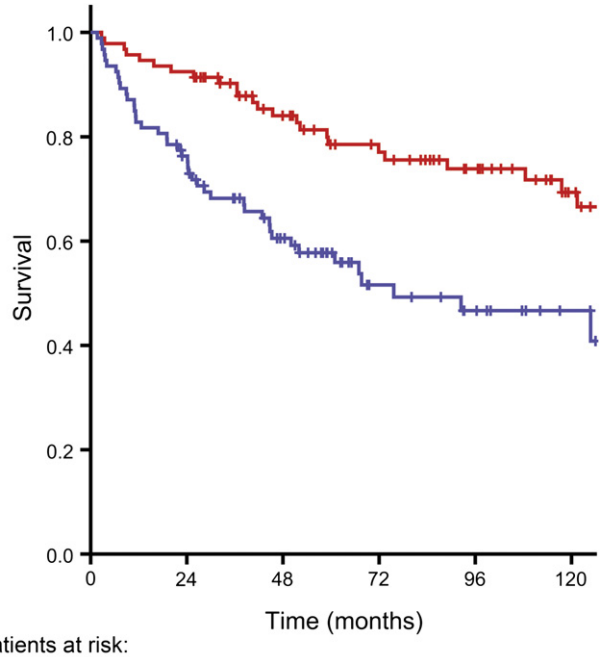
	Perioperative intraperitoneal chemotherapy			Histopathological differentiation			
	EPIC ($n = 48$)	HIPEC ($n = 45$)	p-value	DPAM ($n = 57$)	PMCA-I ($n = 15$)	PMCA ($n = 21$)	p-value
Age	55 (25–76)	57 (24–74)	0.60[c]	52 (24–76)	57 (39–70)	61 (27–73)	0. 60[d]
Gender							
Female	34	33	0.82[a]	43	10	14	0.41[b]
Male	14	12		14	5	7	
Histopathological differentiation							
DPAM	32	25	0.32[b]	–	–	–	–
PMCA-I	7	8		–	–	–	
PMCA	9	12		–	–	–	
Prior surgery score							
PSS-0	3	11	0.23[b]	6	4	4	0.47[b]
PSS-1	15	10		16	2	7	
PSS-2	27	19		32	6	8	
PSS-3	3	5		3	3	2	
Peritoneal cancer index							
PCI ≤10	21	10	0.32[b]	25	3	3	<0.01[b]
PCI 11–20	9	20		19	3	7	
PCI ≥21	18	15		13	9	11	
Peritoneal cancer index, maximum							
PCI_{max} ≤10	12	8	0.44[b]	17	1	2	0.02[b]
PCI_{max} 11–20	13	12		16	3	6	
PCI_{max} ≥21	23	25		24	11	13	
Number of peritonectomy procedures							
0–1	15	14	0.22[b]	23	3	3	<0.01[b]
2–4	16	24		26	4	10	
5–6	17	7		8	8	8	
Days in hospital	16 (8–161)	14 (6–80)	0.22[c]	14 (7–161)	18 (7–80)	20 (6–134)	0.05[d]
Day in intensive care unit	2 (0–66)	1 (0–61)	0.05[c]	1 (0–66)	2 (0–61)	2 (0–61)	0.20[d]
Duration of surgery	264 (75–1500)	395 (227–881)	0.01[c]	346 (75–1500)	555 (155–835)	505 (95–881)	<0.001[d]
Number of blood transfusions	2 (0–61)	2 (0–25)	0.83[c]	1 (0–61)	4 (0–42)	8 (0–33)	<0.01[d]
Complications							
Total	14	8	0.23[a]	12	5	5	0.66[b]
Anastomotic leak	10	4	0.15[a]	8	2	4	0.73[b]
Bleeding	5	2	0.44[a]	3	1	3	0.24[b]
Miscellaneous	4	4	1.00[a]	5	2	1	0.83[b]

Abbreviations: EPIC = early postoperative intraperitoneal chemotherapy; HIPEC = hyperthermic intraperitoneal chemotherapy; DPAM = disseminated peritoneal adenomucinosis; PMCA-I = peritoneal mucinous carcinomatosis, intermediate features; PMCA = peritoneal mucinous carcinomatosis; PSS = prior surgery score; PCI = peritoneal cancer index; PCI_{max} = peritoneal cancer index, maximum.
[a] Pearson's Chi-Square Test.
[b] Chi-square test, linear by linear association.
[c] Mann–Whitney Test.
[d] Kruskal–Wallis Test.

groups had more peritonectomy procedures performed and more protracted surgery compared with the DPAM group. The groups of patients treated with EPIC and HIPEC were similar with respect to histopathological differentiation, PSS, PCI and PCI_{max}. The prolonged duration of surgery in the HIPEC group can be attributed to intraoperative chemotherapy being part of the surgical procedure.

Associations between histopathology- and PIC-groups and outcome

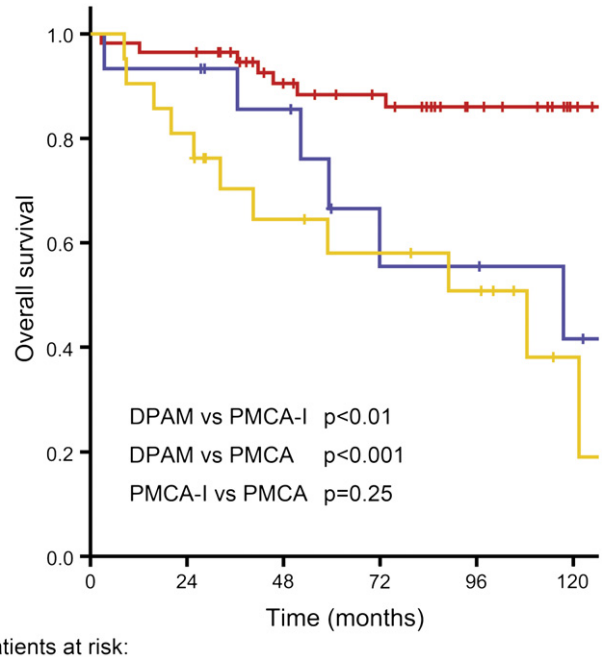
Peritoneal recurrence was diagnosed in 38 patients, out of whom nine additionally developed pleural tumor growth. Treatment of patients with recurrence involved complete CRS and PIC ($n = 8$), complete CRS alone ($n = 5$) and explorative laparotomy or palliative resection ($n = 10$). A total of 25 patients died during the follow-up period; 19 of recurrent disease, three of treatment complications (one after 51 months because of short bowel complications) and three of other causes. The Kaplan–Meier method estimated 5- and 10-year OS of 79% and 69% and DFS of 58% and 47% (Fig. 1). Mean OS was 154 months (95% CI 137–171) and median OS was not reached (follow-up median 85 months (3–207)). Outcome according to histopathological differentiation showed 5- and 10-year OS 88% and 86% in the DPAM group, 67% and 42% in the PMCA-I group and 58% and 38% in the PMCA group (Fig. 2). In 11 patients with PMCA and PCI ≥21, 5- and 10-year OS



Patients at risk:

OS	93	86	65	52	41	26
DFS	93	68	45	22	16	9

Figure 1. Overall survival (red line) and disease-free survival (blue line) in 93 patients with pseudomyxoma peritonei treated with complete cytoreductive surgery and perioperative intraperitoneal chemotherapy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Patients at risk:

DPAM	57	55	43	38	29	21
PMCA-I	15	14	11	5	5	3
PMCA	21	17	11	9	7	2

Figure 2. Overall survival after complete cytoreductive surgery and perioperative intraperitoneal chemotherapy with patients stratified according to histopathological differentiation: disseminated peritoneal adenomucinosis (DPAM; red line, $n = 57$), peritoneal mucinous carcinomatosis of intermediate features (PMCA-I; blue line, $n = 15$) and peritoneal mucinous carcinomatosis (PMCA; yellow line, $n = 21$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

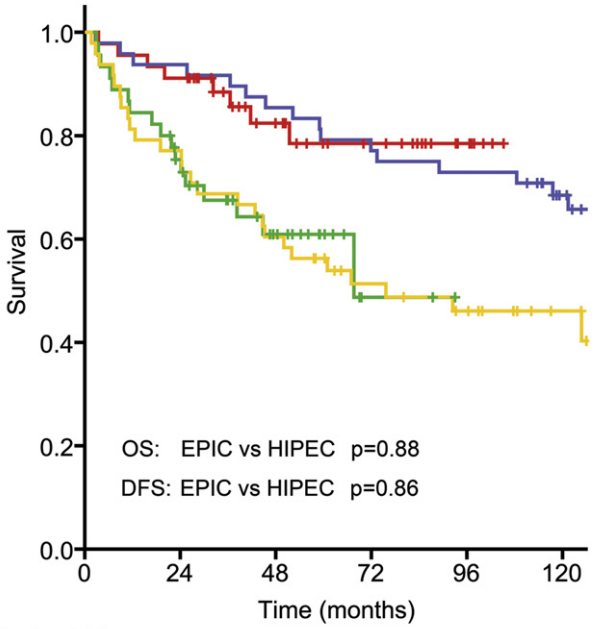
was 49% and 32%. When stratified by mode of PIC, 7-year OS was 75% in the EPIC group versus 79% in the HIPEC group and 7-year DFS was 49% in both groups (Fig. 3). Factors associated with long-term outcome are presented in Table 2. In univariate analysis, low-grade malignancy (DPAM), female gender, low PCI and low PCI_{max} were associated with improved OS and DFS. Low PSS was associated with improved OS but did not influence DFS. Mode of PIC and age, categorized in groups of <55 and ≥ 55 years, did not influence DFS and OS. In multivariate analysis, histopathological differentiation ($p = 0.001$) and gender ($p = 0.045$) were retained as significant factors for OS.

Short-term complications

In the study group, two patients suffered in-hospital death after 84 and 107 days caused by multiple organ failure after anastomotic leak and abdominal sepsis. Twenty-two patients (24%) had complications that required surgery with a total of 46 interventions (1–8 interventions per patient). The main complications were anastomotic leak ($n = 14$) and bleeding ($n = 7$). A positive association was demonstrated between the risk of complications and PCI ($p < 0.001$), PCI_{max} ($p < 0.01$) and male gender ($p = 0.01$), but no such association was found for histopathological differentiation ($p = 0.66$) and mode of PIC ($p = 0.23$).

Discussion

The most noteworthy finding in this study was almost equal long-term outcome in patients treated with EPIC and HIPEC. HIPEC has essentially replaced EPIC as the mode of intraperitoneal chemotherapy in patients with PMP, providing uniformly high drug exposure to the peritoneal surfaces with an assumed augmented anti-tumor effect by hyperthermia.[13] Additionally, the 90-min HIPEC procedure performed under general anesthesia may be viewed as more convenient for the patient than repeated drug instillation for five days. On the other hand, EPIC is less complex and resource-intensive, which may influence availability of the treatment, and although tissue adhesions may limit drug distribution in peritoneal cavity, repeated instillations may offer a more prolonged tissue exposure than in HIPEC. To our knowledge, EPIC and HIPEC in combination with complete CRS have to date not been compared with respect to long-term outcome of PMP. One study revealed a slightly



Patients at risk:

OS:						
EPIC	48	45	41	37	35	26
HIPEC	45	41	24	15	6	-
DFS:						
EPIC	48	37	29	20	16	9
HIPEC	45	31	16	2	-	-

Figure 3. Overall survival and disease-free survival in 93 patients with pseudomyxoma peritonei, stratified according to mode of perioperative intraperitoneal chemotherapy that was administered after complete cytoreductive surgery. The two upper curves demonstrate overall survival in patients that received early postoperative intraperitoneal chemotherapy (EPIC; blue line, $n = 48$) and hyperthermic intraperitoneal chemotherapy (HIPEC; red line, $n = 45$). The two lower curves demonstrate disease-free survival in patients given EPIC (yellow line) and HIPEC (green line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

better survival of PMP with HIPEC compared with EPIC after palliative cytoreduction.[15] In colorectal peritoneal carcinomatosis, HIPEC (oxaliplatin) proved superior to EPIC (MMC, 5-FU) with respect to peritoneal recurrence and complication rate, while OS was not influenced by mode of PIC.[16] An experimental study of EPIC (MMC, 5-FU) and HIPEC (MMC) in a rodent model of colorectal peritoneal carcinomatosis demonstrated no differences in survival.[17] In the absence of randomized trials, comparison of EPIC and HIPEC in the treatment of PMP must rest on retrospective studies. In the present study, the EPIC and HIPEC groups were similar with respect to number of patients, age and gender distribution, histopathological differentiation, extent of previous surgery and tumor distribution (Table 1). A factor that probably influenced the comparison was the assumed effect of a learning curve for CRS which would favor the HIPEC group.[18] In summary, almost equal OS and DFS between the groups suggest that both EPIC and HIPEC in combination with complete CRS offer efficacious treatment of PMP.

For patients with PMP treated with complete CRS and PIC, histopathological differentiation will usually be the most important prognostic factor.[7,19,20] Given the excellent long-term survival generally observed in patients with DPAM, conducting extensive treatment in these patients is uncontroversial. In contrast, because aggressive histology is associated with a less favorable prognosis, an approach in keeping with recommendations for peritoneal carcinomatosis from colorectal cancer has been advocated in these cases.[21] In patients with colorectal peritoneal carcinomatosis, a PCI $\geq$21 is taken to indicate that the patient is biologically incurable even when complete CRS is technically possible.[22] However, the reported 5- and 10-year OS of 49% and 32% in patients with PMCA and PCI $\geq$21 that received complete CRS and PIC must be considered an acceptable long-term outcome. Thus, in our opinion, patients presenting with clinical PMP should be approached similarly regardless of histological subgroup: When assessment of tumor distribution at the beginning of the surgical procedure reveals complete CRS to be possible, this should be performed even in patients with aggressive histology and high PCI, and be followed by administration of PIC.

The finding of female gender as a positive prognostic factor for OS was in agreement with one previous report.[21] Except for the higher complication rates in males, including two cases of postoperative mortality, we see no obvious explanation for this result. Whether it represents a general feature of the disease and treatment or is a coincidental finding is uncertain. Because there are no obvious therapeutic implications, it is mainly an interesting observation.

The present study was conducted focusing on the group of patients that actually received complete CRS and PIC. In peritoneal surface malignancies, the imaging techniques available are rather inaccurate and CT scan, the radiological examination modality most commonly used in preoperative work-up, tends to underestimate the tumor distribution.[23] Therefore, patients with too extensive disease for complete CRS may not be recognized by preoperative work-up and will undergo explorative and/or debulking procedures. If such cases are included in the survival analyses together with patients that receive complete CRS and PIC, the efficacy of multimodal treatment will be underestimated.[8] Because complete CRS is a cornerstone of multimodal treatment of PMP, the degree of cytoreduction will in such analyses usually be the only significant prognostic factor and other important parameters for survival may be lost.[5,6] Thus, to accurately evaluate the efficacy of multimodal treatment and to identify predictive factors for therapy response, instead of using intention-to-treat approach only, separate analyses should be performed on the subgroup that actually receive complete CRS and PIC.

Table 2
Survival analysis according to clinicopathological parameters.

	Univariate analysis (*P*-values, log-rank test)		Multivariate Cox regression analysis for overall survival		
	Disease-free survival	Overall survival	*P*-values	Hazard ratio	95% CI
Age	0.75	0.11			
<55					
≥55					
Gender	0.001	0.01	0.045		
Female				–	
Male				2.3	1.0–5.0
PIC	0.86	0.88			
EPIC					
HIPEC					
Histology	<0.01	<0.001	0.001		
DPAM				–	
PMCA-I				4.1	1.4–12.4
PMCA				6.3	2.5–16.3
PSS	0.29	0.04			
PSS-0					
PSS-1					
PSS-2					
PSS-3					
PCI	<0.001	<0.001			
PCI ≤10					
PCI 11–20					
PCI ≥21					
PCI_{max}	<0.001	0.03			
PCI_{max} ≤10					
PCI_{max} 11–20					
PCI_{max} ≥21					

Abbreviations: CI = confidence interval; PIC = perioperative intraperitoneal chemotherapy; EPIC = early postoperative intraperitoneal chemotherapy; HIPEC = hyperthermic intraperitoneal chemotherapy; DPAM = disseminated peritoneal adenomucinosis; PMCA-I = peritoneal mucinous carcinomatosis, intermediate features; PMCA = peritoneal mucinous carcinomatosis; PSS = prior surgery score; PCI = peritoneal cancer index; PCI_{max} = peritoneal cancer index, maximum.

Conclusions

Patients treated with complete CRS and PIC achieved satisfactory long-term outcome, in accordance with results in previous reports. The most important prognostic factor for OS was histopathological differentiation, but acceptable long-term outcome was observed after multimodal treatment even in patients with aggressive histology and extensive intraperitoneal tumor distribution. Almost equal survival rates for patients treated with EPIC and HIPEC suggest that efficacious treatment of PMP can be achieved even with a less resource-intensive technique than the one currently considered as the treatment of choice.

Conflict of interest

The authors declare that they have no competing interests.

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Helsedirektoratet God helse - gode liv

National guidelines
Exclusion criteria in colorectal cancer

1. Central lymph node metastases
2. Not-resectable organ metastases
3. Alder > 75 år
4. General carcinomatosis on major parts of the small bowel
5. PCI over 20-25
6. ECOG performance status ≥ 2-3
7. Major comorbidity
8. Tumour progression during chemoterapy
9. Signet-ring-cell differensiation
10. Major adhesions

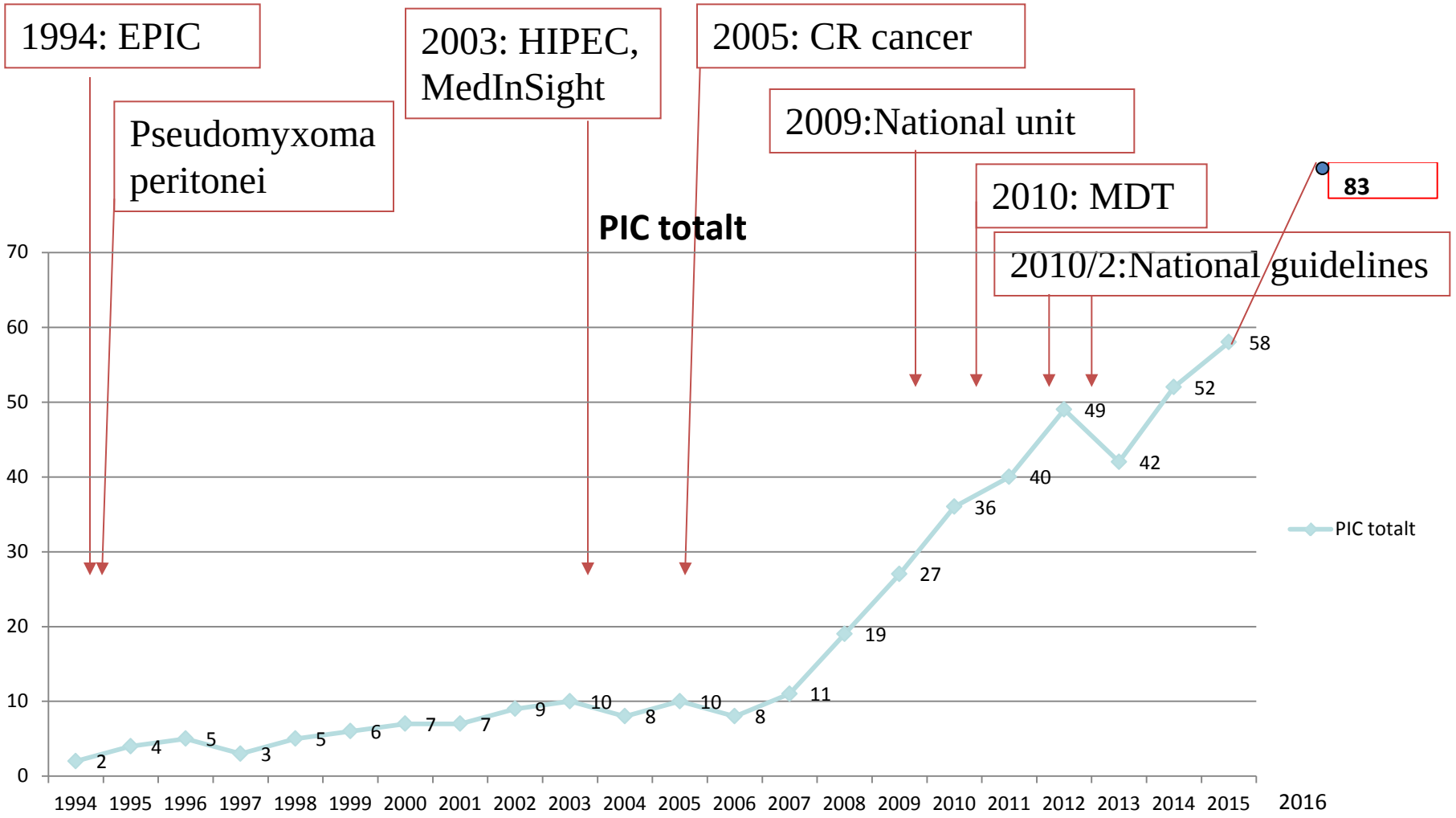
Helsedirektoratet God helse - gode liv

Nasjonal retningslinjer

HIPEC ved synkrone peritoneale metastaser er mindre aktuelt dersom:

1. Alder er høy.
2. Forekomst av radiologisk maligne lymfeknuter
3. Tegn på subileus/ ileus
4. Levermtastaser +/- lungemetastaser

Development DNR 1994 -2016



other reasons (n = 12). Thus, 144 patients were treated with CRS-HIPEC, from which another 18 patients with appendiceal cancer were excluded from the study, as well as seven patients without histologically verified PM at primary surgery or at the time of CRS-HIPEC. The remaining 119 patients constitute the study population.

All patients treated surgically for PM-CRC at the Norwegian Radium Hospital were prospectively registered in the institutional peritoneal surface malignancy database where information regarding clinicopathological data, treatment details, and outcome were recorded. The study cohort was identified from this registry according to criteria presented above. Missing data were retrospectively collected from patient records, and in particular, all pathology reports from referring hospitals were collected and reexamined. Information regarding disease recurrence was obtained by retrieving patient records and radiologic work-up from referring hospitals where patients received postoperative follow-up. Survival data was obtained from the Norwegian National Registry on June 8, 2015 and patients alive at this date were censored. Synchronous PM was defined as PM at or within 6 months of primary surgery and the disease-free interval (DFI) was defined as the time from primary surgery to PM diagnosis [10]. The study was approved by the Norwegian Ethics Committee (s-07160b) and written informed consent was obtained.

Treatment

CRS was performed with the intention to remove all macroscopically visible tumor, involving peritonectomy procedures, and organ resections as necessary [11]. Peritoneal tumor distribution was classified using the peritoneal cancer index (PCI) [12]. The completeness of cytoreduction (CC) score was used to evaluate residual tumor after CRS: CC-0, no tumor; CC-1, tumor < 2.5 mm; CC-2, tumor 2.5–25 mm; CC-3, tumor > 25 mm [12]. When complete cytoreduction (CC-0 or CC-1) was achieved, HIPEC with mitomycin C 35 mg/m^2 (maximum 70 mg) was administered using an open Coliseum technique until 2008, and thereafter a closed technique with open abdomen [13]. Mitomycin C was added to saline 0.9% and administered for 90 min in three fractions (50%—0 min, 25%—30 min, and 25%—60 min). Median procedure duration was 378 min (245–880), median perfusion flow rate was 3.3l/min (1.0–4.2), and median temperature (intraperitoneal measurements) was 41.4°C (39.5–42.1). All anastomoses were completed before the HIPEC procedure. CRS-HIPEC was most often performed as a single procedure, but 16 patients received HIPEC in a second procedure, usually within 1 week after CRS. Adjuvant chemotherapy was not routinely given. Postoperative complications (30-day morbidity and 100-day mortality) were classified according to the Clavien–Dindo Classification of Surgical Complications [14].

Statistical Analysis

Categorical variables were described using frequencies/percentages and continuous variables were described with median/range. Univariate analysis was performed using the Kaplan–Meier method, with survival time from CRS-HIPEC to death or censoring date June 8, 2015 (OS) and from CRS-HIPEC to the time of recurrence (peritoneal relapse and/or distant metastasis), new primary cancer, death or last follow-up [disease-free survival (DFS)]. The log-rank test was used to compare differences in survival. Factors significant and borderline significant in univariate analysis were further examined using multivariable Cox proportional hazards regression, in addition to age and localization of primary tumor. Performance status was registered only for the latter half of the patient population, and therefore not included in multivariable analysis. The accuracy of PCI for prediction of long-term outcome was investigated by receiver operating characteristic (ROC) curve analysis, and time-dependent ROC curve analysis (supplementary material) [15]. P-values < 0.05 were considered statistically significant. Statistical analyses were conducted using SPSS software (version 22.0, SPSS, Inc., Chicago, IL) and R software (survivalROC version 1.0.3).

RESULTS

Table I summarizes clinicopathological characteristics of the study cohort, which comprised 77 women (65%), and 42 men (35%) with median age 58 years (22–77). Colon (n = 109) was the most common localization for the primary tumor and PM was synchronous in 73 patients. Sixty patients were diagnosed with IUCC stage IV disease after primary surgery, almost exclusively in the form of PM alone (n = 58) [PM and liver metastasis (n = 1), and isolated liver metastasis (n = 1)]. Metachronous PM occurred median 15 months (7–67) after primary surgery and the DFI was less than 18 months in the majority of patients (86%). The median time from first diagnosis of PM to CRS-HIPEC was 4 months (0–45). The primary tumors were classified as moderately differentiated adenocarcinomas in 56%, while 28% were poorly differentiated, and 7% were well differentiated. Signet ring cells were present in 12% of the primary tumors, and 28% were mucinous adenocarcinomas. Sixty-eight percent had received chemotherapy at some point prior to CRS-HIPEC, and performance status was in most cases ECOG 0 (n = 50), while seven patients were ECOG 1.

Surgical Treatment and Short-Term Outcome

Median PCI at the time of CRS-HIPEC was 9 (0–28), and approximately 2/3 of the patients had PCI between 0 and 10 (62%), while only 10 patients (8%) had PCI > 20. Three patients had no visible peritoneal tumor at the time of HIPEC (PCI 0), but had histologically verified PM that was removed at the time of primary surgery. A prerequisite for administering HIPEC was CC-0 (n = 113) or CC-1 (n = 5).

Eighteen patients experienced one or more severe complication, where the most severe complication corresponded to grade IIIa (n = 7), IIIb (n = 10), and IVa (n = 1). The complications were as follows; intraabdominal abscess (n = 9), digestive fistula (n = 3), anastomotic- or bowel-leakage (n = 3), pancreatic fistula and/or leakage (n = 2), wound dehiscence (n = 2), bowel obstruction (n = 1), liver failure (n = 1), hemorrhage (n = 2), and pleural effusion (n = 1). Ten of the 18 patients required surgical intervention, representing 8% of the total patient population. The remaining complications were resolved by endoscopic or interventional radiologic procedures. There was no mortality within the first 100 days of surgery.

Long-Term Outcome

The estimated 3- and 5-year OS were 65% and 36%, respectively, and estimated median OS was 47 months (95%CI 42–52). Median follow-up was 45 months (95%CI 35–55). Estimated median DFS was 10 months (95%CI 7–12), with a median follow-up of 42 months (95% CI 32–51). Three-year estimated DFS was 21% and 5-year DFS 14% (Fig. 1a).

In univariate analysis PCI ≤ 10 (Fig. 1b) and ECOG-status < 1 was associated with improved OS and DFS (Table II). Patient age, prior chemotherapy, primary tumor IUCC stage, histological grade, and localization were not associated with outcome in this cohort. Women had significantly superior DFS to men ($P < 0.001$), and borderline longer OS ($P = 0.08$). No treatment-related factors were associated with outcome, including timing of removal of the primary tumor, operating time, and perfusate temperature. There was no difference in outcome

TABLE I. Clinicopathological Characteristics, Procedure Details and Outcome for 119 Patients Treated With CRS-HIPEC for PM-CRC

Variable	N (%)
Patient	
Gender	
Female	77 (65)
Male	42 (35)
Median age, years (range)	58 (22–77)
Performance status	
ECOG 0	50 (42)
ECOG 1	7 (6)
ND	62(52)
Prior chemotherapy	
No	38 (32)
Yes	81 (68)
Primary tumor	
Localization	
Colon	109 (92)
Rectum	10 (8)
T-stage	
pT1	1 (1)
pT3	54 (45)
pT4	63 (53)
ND	1 (1)
N-stage	
pN0	34 (29)
pN1	41 (35)
pN2	42 (35)
ND	2 (2)
Number of lymph nodes examined	
<12	30 (25)
≥12	89 (7)
ND	1 (1)
Tumor differentiation	
Poor	33 (28)
Moderate	67 (56)
Well	8 (7)
ND	11 (9)
Presence of signet ring cells	
No	104 (87)
Yes	14 (12)
ND	1 (1)
Mucinous	
No	85 (71)
Yes	33 (28)
ND	1 (1)
Synchronous PM	
Yes	73 (61)
No	46 (39)
Median DFI, months (range)	15 (7–67)
DFI	
<18 months	102 (86)
≥18 months	16 (13)
ND	1 (1)
Procedure	
Median PCI (range)	9 (0–28)
PCI	
0–10	74 (62)
11–20	35 (29)
>20	10 (8)
Completeness of cytoreduction	
CC-0	113 (95)
CC-1	5 (4)
ND	1(1)
Outcome	
Median hospital stay, days (range)[a]	10 (5–57)
Postoperative complications	
None/mild/moderate	101 (85)
Severe	18 (15)
100-day mortality	0 (0)
Overall mortality	61 (51)
First recurrence	
No recurrence	23 (19)
PM only	32 (27)
PM and distant metastasis	30 (25)
Distant metastasis only	33 (28)
ND	1 (1)

Data are expressed in n (%) unless otherwise specified. CRC, colorectal cancer; CRS, cytoreductive surgery; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermicintraperitoneal chemotherapy; ND, not determined; PCI, peritoneal cancer index; PM, peritoneal metastasis.

[a]Hospital stay at Norwegian Radium Hospital.

between patients obtaining CC-0 and CC-1 and occurrence of severe postoperative complications did not affect OS or DFS.

Ninety-five patients (80%) experienced disease recurrence; with PM only (n = 32), PM and distant metastasis (n = 30), and distant metastasis only (n = 33) as the first registered recurrence. Organ specific localizations of the distant metastasis were as follows: liver (n = 13), lung (n = 17), lymph nodes (n = 14), thoracic wall (n = 1), adrenal gland (n = 1), and multiple sites (>1 site) (n = 17). Patients with distant metastasis only had an estimated 5-year OS of 53% from the time of CRS-HIPEC, while for patients with peritoneal relapse with or without metastasis 5-year OS was 19% ($P = 0.002$). Patients with peritoneal relapse with or without metastasis had a median OS of 22 months from the time of recurrence, compared to 44 months for patients with distant metastasis only ($P = 0.001$).

PCI ($P = 0.015$) emerged as sole predictor of OS in multivariable analysis, with a hazard ratio of 1.05 (95%CI 1.01–1.09) for every increase in PCI, while predictors of DFS were PCI ($P < 0.0001$) and gender ($P = 0.01$; Table III). Since one of the recurring questions in the field concerns to what extent PCI can be used to select patients for CRS-HIPEC, the ability of PCI to predict disease relapse was evaluated by ROC-curve analysis, and time-dependent ROC curve analysis (supplementary material). The AUC (area under the curve) was 0.82 (95%CI 0.74–0.91) for prediction of relapse ($P < 0.0001$; Fig. 2). The highest accuracy for PCI on predicting relapse was obtained for PCI = 7.5, giving a sensitivity of 72%, a specificity of 78%, a PPV of 93% (69 of 74), and a NPV of 40% (18 of 45). More interestingly, PCI > 12 yielded 100% specificity for development of disease relapse.

DISCUSSION

The present work describes short- and long-term outcome and associated prognostic factors for all patients treated with CRS-HIPEC for non-appendiceal PM-CRC in Norway between 2004–2013 (n = 119). Five-year OS was 36% with a median OS of 47 months, which is in concordance with published results from other tertiary referral centers [5,8,16]. In comparison, for patients with limited PM receiving contemporary systemic chemotherapy with or without palliative surgery, a considerably shorter median OS of 17–24 months has been reported [6,7], which is also the finding of a recent meta-analysis [16]. At this point it is however impossible to know whether these results are attributable to CRS-HIPEC or CRS alone, a question that can only be answered by randomized controlled trials. Interestingly, a French group recently reported 5-year OS of 44% and median OS of 48 months in a comparable group of PM-CRC patients without liver or lung metastasis that were treated with CRS and systemic chemotherapy [17], while a recent Chinese case-control study found significantly better OS in the CRS-HIPEC group (n = 33) compared to the CRS-only group (n = 29) [18]. The results from the PRODIGE7 randomized trial comparing CRS to CRS-HIPEC (ClinicalTrials.gov identifier: NCT00769405) are naturally much awaited.

Even though CRS-HIPEC offers the possibility of improved outcome in PM-CRC, approximately 50% of patients will experience disease recurrence within the first year [19–21], which was also the case in our cohort. The time from recurrence until death may reflect disease aggressiveness and treatment response, and can be explored by determining the ratio between OS and progression-free survival (PFS) [22] or DFS. In this study, an OS/DFS-ratio of 4.8 can be calculated, while in metastatic CRC treated with 1.line chemotherapy OS/PFS-ratios of 1.7–3.2 can be determined from results published in a recent comprehensive review [23]. This suggests that CRS-HIPEC is beneficial to patients by improving OS despite the relatively short DFS. Of patients with recurrence, 1/3 recurred with distant metastasis only, which was associated with better outcome than patients with peritoneal relapse (alone or in combination with distant metastasis).

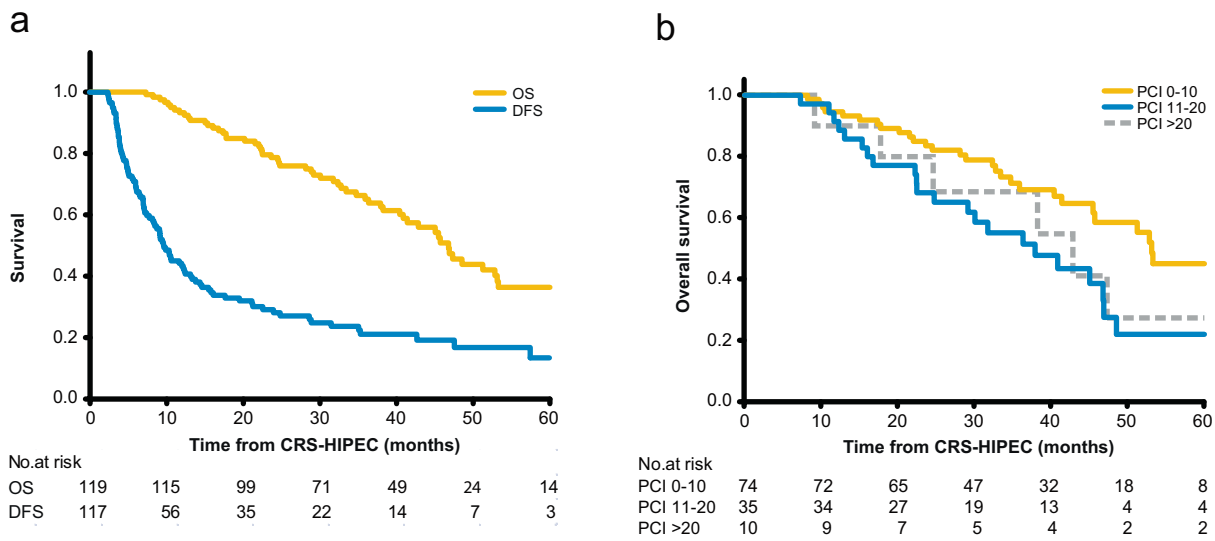


Fig. 1. Survival curves after cytoreductive surgery (CRS) and HIPEC in patients with peritoneal metastases from colorectal cancer (**a**) Overall survival (OS) and disease-free survival (DFS) (**b**) Peritoneal cancer index (PCI) and OS.

TABLE II. Univariate Analysis of OS and DFS After CRS-HIPEC in Patients With PM-CRC

Variable	OS	*P*	DFS	*P*
Gender				
Female	47	0.08	13	<0.001[c]
Male	41		8	
Synchronous PM				
Yes	47	0.67	9	0.25
No	46		12	
Localization primary tumor				
Colon	47	0.31	10	0.47
Rectum	22		9	
N-stage primary tumor				
N0	46	0.55	12	0.86
N1, N2	47		9	
Number of lymph nodes examined				
<12	38	0.09	9	0.59
≥12	47		10	
Tumor differentiation (primary)				
Poor	46	0.58	8	0.40
Moderate/well	47		10	
Prior chemotherapy				
No	49	0.56	9	0.96
Yes	47		10	
Performance status				
ECOG 0[a]	—	0.001	11	0.014
ECOG 1	17		5	
DFI 18 months				
<18 months	46	0.27	9	0.03
18 + months	53		24	
PCI				
0–10	53	0.03[c]	13	<0.0001[c]
11–20	38		7	
>20	43		7	
First recurrence				
PM with/without distant metastasis	36	0.002	8	0.56
Distant metastasis only[b]	—		6	

Median OS and DFS are expressed in months. CRC, colorectal cancer; CRS, cytoreductive surgery; DFI, disease-free interval; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival; PCI, peritoneal cancer index; PM, peritoneal metastasis.
[a,b]Median OS not reached.
[c]Variable also significant in multivariable analysis.

Patients with distant metastasis only may be eligible for curatively intended interventions, which could contribute to improved outcome. However, also the patient subgroup receiving palliative chemotherapy or best supportive care for distant metastases had a trend towards superior OS compared to those with peritoneal relapse (data not shown), which is in accordance with previous studies [1,24,25], suggesting a difference in disease biology that is currently not clearly understood.

Short-term outcome after major surgery may reflect how successfully a treatment has been implemented in a surgical center. There was no 100-day mortality in this cohort, and the incidence of severe postoperative complications was 15%, with a re-operation rate of 8%, suggesting that the treatment was well tolerated. In larger patient series (n > 100), postoperative mortality rates between 0.7% and 7.7% have been reported [20,21,25–30], and re-operation rates vary between 4% and 20.8% [8]. Abscess- or fistula-formation and anastomotic-or bowel-leakage were the most frequent complications, similarly to what others have reported [8]. Taken together, for eligible patients CRS-HIPEC seems to be a well-tolerated procedure.

The search for prognostic factors that could improve selection of patients for CRS-HIPEC is constantly ongoing. No associations were found between primary tumor characteristics and outcome, which is in contrast to some reports, but in accordance with others, since results regarding factors associated with outcome vary considerably. For instance, primary tumor differentiation was not associated with outcome in some studies [19,21], whereas a clear association with OS in multivariable analysis was reported by others [20]. In this cohort, univariate analysis identified performance status as a strong prognostic factor, which is interesting, even though the ECOG 1 group was small. Having a DFI of more than 18 months was associated with improved DFS, which could reflect favorable tumor biology. Female gender was positively associated with DFS ($P < 0.001$) and OS ($P = 0.08$), which has been shown before [20,25,31]. A higher incidence of PM-CRC in women has also been previously reported [32], but the reason for the apparent gender differences in incidence and outcome is not clear.

The parameter most consistently associated with long-term outcome after CRS-HIPEC for PM-CRC in addition to completeness of cytoreduction, is PCI, which was also the only parameter that

TABLE III. Multivariable Analysis of OS and DFS After CRS-HIPEC for Patients With PM-CRC

	OS		DFS	
Variable	HR (95%CI)	*P*	HR (95%CI)	*P*
PCI (continuous variable)	1.05 (1.01–1.09)	0.015	1.06 (1.03–1.10)	<0.0001
Gender (ref female)	1.52 (0.89–2.57)	0.12	1.78 (1.14–2.77)	0.01
Examined lymph nodes (continuous variable)[a]	0.98 (0.95–1.02)	0.37	—	—
Age	0.99 (0.96–1.01)	0.25	1.00 (0.98–1.02)	0.77
DFI 18 months (ref DFI > 18 mo)[b]	—	—	1.89 (0.97–3.71)	0.06
Primary tumor localization (ref colon)	1.84 (0.77–4.42)	0.17	0.93 (0.39–2.23)	0.87

CRC, colorectal cancer; CRS, cytoreductive surgery; DFI, disease-free interval; DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival; PCI, peritoneal cancer index; PM, peritoneal metastasis.
[a,b]Variable not included in multivariable analysis of DFS and OS, respectively.

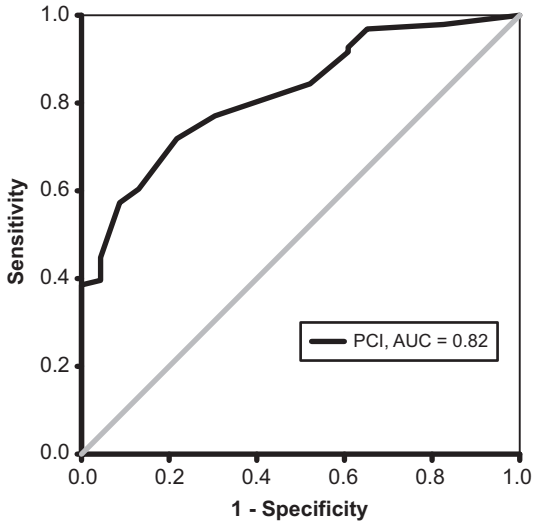


Fig. 2. ROC curve analysis of peritoneal cancer index (PCI) and recurrence after cytoreductive surgery and HIPEC in patients with peritoneal metastases from colorectal cancer. AUC, Area under the curve.

remained associated with both OS and DFS in multivariable analysis in this cohort. In a French study of 173 patients, a linear correlation was found between PCI and OS, and based on these results PCI 12–17 and PCI > 17 were recommended as relative and absolute contraindications for CRS-HIPEC, respectively [33]. Using ROC-curve analysis in our study, a cut-off value of PCI > 12 corresponded to 100% specificity for prediction of disease recurrence, in accordance with these recommendations above [33]. PCI > 20 has in many centers, ours included, been regarded as a relative contraindication to CRS-HIPEC for PM-CRC [19,34,35]. However, we found no difference in long-term outcome for patients with PCI 11–20 and PCI > 20, and the long OS observed for patients with PCI > 20 could indicate that CRS-HIPEC should also be considered in select patients with resectable extensive disease, in accordance with another report [36]. Thus, it seems that although PCI is clearly associated with long-term results, establishing a PCI cut-off value is still challenging.

CONCLUSIONS

Following CRS-HIPEC, patients achieved 5-year OS and DFS of 36% and 14%, respectively, with no mortality and acceptable morbidity, which is in line with published reports. OS was considerably longer than the DFS, warranting increased focus on the treatment regimen following disease relapse to improve our understanding of PM biology. Peritoneal disease burden, expressed by the PCI, was the only factor associated with OS in multivariable analysis, and ROC-analysis suggested a PCI cut-off > 12 to identify patients at high risk of disease recurrence. In conclusion, the possibility of long-term survival combined with acceptable postoperative morbidity and mortality leave CRS-HIPEC as an important treatment option for eligible patients with resectable PM-CRC.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

SYNOPSIS

Oncologic outcome and associated prognostic factors in a national cohort study comprising all patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for non-appendiceal colorectal peritoneal metastasis in Norway between 2004 and 2013.

13.1.6 Prognostiske faktorer

Økende antall lungemetastaser, samt kort tid fra diagnose av primærtumor til påvisning av lungemetastase(r) påvirker prognosen negativt (381;382) Ut over dette er det ikke påvist selvstendige, statistisk signifikante faktorer som predikerte overlevelse (377).

Tom Treasure har foretatt en kritisk vurdering av dokumentasjonen for lungemetastasekirurgi og satt opp prognostiske forhold knyttet til overlevelse etter pulmonal metastasektomi (383):

Forhold som påvirker overlevelse	Fordelaktig	Intermediært	Negativt
Tid siden primær-operasjon	> 36 måneder	12 – 36 måneder	0–12 måneder
Antall metastaser	1	2–5	> 5
Affeksjon av 1 eller 2 lunger	Unilateral	Bilateral	Bilateral
CEA-verdi	< 5	5 – 10	> 10
Levermetastaser	Ingen	Operativt fjernet	Tilstede

Denne oversikten er også i tråd med vår oppfatning av at økende multiplisitet og spredning er uttrykk for dårlig prognose. For ytterligere fordyping anbefales to oversiktsartikler (384;385).

Anbefalinger

- Inntil resultater av kontrollerte undersøkelser foreligger, anbefales det at lungemetastaser fra tykk- og endetarmskreft kan opereres (evidensgrad C).
  - Som hovedregel bør rekkefølgen være at lungemetastaser opereres sist.
  - Forutsetninger for operativ behandling er at:
    - Det ikke foreligger kreftsykdom utenfor lungene.
    - Alle metastaser kan fjernes radikalt.
  - Forhold som svekker indikasjon for operasjon for lungemetastase:
    - Kort tid fra behandling av primærtumor til funn av lungemetastase.
    - Flere lungemetastaser.
    - Engasjement av flere lungelapper.
    - Forhøyet CEA.
    - Levermetastaser.
    - Påviste lymfeknutemetastaser i lungehilus.

13.2 Behandling av peritoneal karsinomatose med maksimal cytoreduktiv kirurgi og hyperterm intraperitoneal kjemoterapi

Behandlingen av peritoneal karsinomatose (peritoneale metastaser) har endret seg fra palliasjon til en aggressiv, aktiv behandling (386). Maksimal cytoreduktiv kirurgi (CRS) med etterfølgende hyperterm intraperitoneal kjemoterapi (HIPEC) er en lovende behandling for peritoneal karsinomatose og har gitt pasienter med begrenset tumorutbredelse i peritoneum en mulighet for helbredelse. Overlevelsen ved kirurgi for karsinomatose hos selekterte pasienter er omtrent

som etter leverreseksjoner eller lungereseksjoner for colorectale metastaser. Behandlingen gis i Norge på Oslo universitetssykehus, Radiumhospitalet.

13.2.1 Hyppighet

Cirka 5 % av pasienter med primær tykk- og endetarmskreft har karsinomatose ved diagnosetidspunktet, og ved residiv har 25 % karsinomatose (387;388). Opptil halvparten av pasientene er uten samtidige systemiske metastaser (389). Sannsynligvis bør 3 % av pasienter med colorectal cancer vurderes for behandlingen (ca. 100/år i Norge). I 2013 ble det gjort CRS-HIPEC på mer enn 50 pasienter ved Oslo universitetssykehus, Radiumhospitalet. Nær 80 % av pasientene hadde colorectal cancer som utgangspunkt, de resterende pseudomyxom.

13.2.2 Klassifikasjon

Peritoneal cancer indeks (**Error! Hyperlink reference not valid.**) brukes til å beskrive utbredelsen av sykdommen i 9 bukregioner og 4 avsnitt av tynntarm. Den er en viktig prognostisk faktor for komplett cytoreduksjon og prognose (**Error! Hyperlink reference not valid.**). Sykdommen lokaliseres særlig til steder for drenasje av ascitesvæske (paracolisk på begge sider, over lever, i det store oment og mot ventrikkelens majorside). Tyngdekraften fører til at bekkenet også er hyppig lokalisasjon mens tynntarm lenge er spart pga. tarmbevegelse.

13.2.3 Dokumentasjon av behandlingen

I en randomisert studie mellom peritonektomi med HIPEC og onkologisk behandling (5FU og Leukoverin) fra 2003 var median overlevelse etter peritonektomi cirka 22 mnd. og ved onkologisk behandling 12 mnd (390) (Evidensgrad A). Moderne systemisk kjemoterapi har bedret overlevelsen, men 5-års overlevelse er sjelden (391). I flere andre rapporter har 5-års overlevelsen ved CRS-HIPEC vært 30–45 % (390;392;393) (Evidensgrad B). Tre faktorer er funnet å være viktige for overlevelse: tumor differensiering, PCI og grad av cytoreduksjon (394). Antall organreseksjoner er ikke funnet å bety noe for overlevelse (395).

13.2.4 Metode

Maksimal cytoreduktiv kirurgi (CRS) (396)

- Ved påvisning av karsinomatose under primæroperasjon av tykk- og endetarmskreft på eget sykehus anbefales at primærtumor fjernes, men at det gjøres minst mulig utløsning av carcinomatose. Tumorvev tenderer til å vokse fast i fibrøse adheranser og vanskeliggjør endelig kirurgi. Aktuelle pasienter bør henvises til Oslo universitetssykehus for CRS med HIPEC.
- Resultatene er best om pasienten henvises når carcinomatose oppdages, og ikke etter at kjemoterapi har sviktet (392).

- Second-look operasjon 6–12 mndr. etter primæroperasjonen bør vurderes hos asymptomatiske pasienter i god almentilstand som primært fikk utført antatt kurativ operasjon, men som man vet har høy risiko for utvikling av peritoneal carcinomatose, nemlig ved (397):
  - iatrogen perforasjon i tumorområdet
  - metastaser til ovarier
  - carcinomatose makroscopisk radikalt fjernet ved primæroperasjon

Eventuell second-look operasjon bør drøftes med Radiumhospitalet; om, når, hvorhen og hvordan slik operasjon skal gjøres.

Prinsippet ved kirurgien er å fjerne all peritoneum parietale med synlig tumor. På tarmen kan små tumorfoci brennes vekk med diatermi. Ved større affeksjon må tarmsegmentet fjernes. En opererer i region for region i buken og fjerner alt synlig tumorvev. Normal peritoneum røres ikke. En starter ofte med omentectomi. Deretter gjøres ofte endelig kirurgi i bekkenet med peritonectomi og reseksjon av rectum og genitalia interna ved behov. Reseksjon av peritoneum i flanker og behov for colonkirurgi vurderes. Deretter vurderes behovet for reseksjon av peritoneum på diafragmakupler, galleblære og milt. CRS-inngrep tar ofte 6–8 timer før etterfølgende HIPEC. Reoperasjoner på grunn av infeksjoner, tarmslyng eller lekkasjer kan bli nødvendig. Median liggetid på Radiumhospitalet er 9 dager etter operasjon, men kan hos enkelte være betydelig lenger.

13.2.5 Hyperterm intraperitoneal kjemoterapi (HIPEC)

Dersom en oppnår maksimal cytoreduksjon (CC 0–1) gis det HIPEC enten som direkte fortsettelse av operasjonen eller kort tid seinere.

Ved å administrere cytostatika intraperitonealt kan konsentrasjonen i skyllevæsken økes i forhold til om det ble gitt intravenøst. For å forsterke effekten av cytostatika varmes denne opp slik at væsken i bukhulen holder 41–42 °C. Mitomycin C (35 mg/m2, maks 70 mg) brukes vanligvis. Denne cellegiften har mange gunstige farmakokinetiske egenskaper ved intraperitoneal bruk, hemmer DNA syntesen i kreftcellene og har økt cytotoksisk virkning ved oppvarming (398). Cellegiften gis i 90 minutter og prosedyren øker operasjonstiden med ca. 3 timer. En bruker en hjerte-lunge-maskin til å distribuere cellegiften i bukhulen og for å oppnå ønsket temperatur.

13.2.6 Inklusjonskriterier for CRS-Hipec

- Begrenset peritoneal karsinomatose uten annen systemisk kreftsykdom, ved synkron eller metakron colorektal cancer
- Mucinøs intraabdominal tumorutbredelse fra appendix vermiformis (pseudomyxoma peritonei (PMP)), uavhengig av tumorutbredelse
- Ved abdominalt mesoteliom
- Vedr second-look ved colorectal cancer – se pkt 13.2.4

13.2.7 Eksklusjonskriterier

- sentrale glandelmetastaser etter utredning ved bruk av CT, MR, evt. PET eller laparoscopi
- ikke-resektable organmetastaser
- generell karsinomatose på større avsnitt av tynntarmen (gjelder ikke v. PMP)
- Peritoneal Cancer Index (PCI) (386) over 20–25 (gjelder ikke v. PMP)
- alder > 75 år
- ECOG performance status ≥ 3
- betydelig komorbiditet
- tumorprogresjon under pågående kjemoterapi
- utilgjengelig bukhule
- signetringcelledifferensiering er en relativ kontraindikasjon
- alder > 75 år er en relativ kontraindikasjon

av pasienter til behandlingstjenesten blir publisert der. Behandlingsskjemaer på nettet kan muligens gi oss mer komplette søknader, og dermed unngå unødvendig behandlingsutsettelser. http://www.oslo-universitetssykehus.no/omoss_/avdelinger_/hyperterm-intraperitoneal-kjemoterapi-ved-kolorektal-kreft-psudomyksoma-peritoneii-og-peritonealt-mesoteliom_

A. Undervisning: Utdanningen er særlig knyttet til opplæring av personell som samarbeider tett mot behandlingstjenesten og til informasjon mot samarbeidende sykehus og avdelinger. En del innlegg i kirurgisk og onkologisk miljø.

B. Faglig opplæring i praksis:

- Kolleger som ønsker mottas og deltar ved kirurgi og på tverrfaglig behandlingsmøte (MDT)

C. Formidling til pasienter/ pårørende:

- Innlegg på 3 pasientkurs om mage-tarmkreft på Montebellosenteret, Mesnali (40 x 3 pasienter/ pårørende).
- Egen hjemmeside internett under OUS. 2015.

D. Formidling til almenheten: Kreftlex- Pasientinformasjon med svært mange treff.

E. Kvalitetsverktøy:

- Nasjonalt handlingsprogram for tykk- og endtarmskreft (Helsedirektoratet), oppdat. 2015 , 2012,
- Metodebok gastrokirurgi, OUS, 2015, 2015,
- Regional retningslinje Oncolex. Elektronisk kreftleksikon utviklet på Radiumhospitalet, 2013,
- Nasjonal retningslinje MedInSight. Prospektiv database peritoneal cancer med 1300 pasienter, 2003,
- Nasjonalt medisinsk kvalitetsregister Biobank av tumorvev og blod fra alle pasienter som samtykker, 2012, Biobank

F. Artikler 2016

Flatmark K, Saelen MG, Hole Kh, Abrahamsen TW, Fleten KG, Hektoen HH, Redalen KR, Seierstad T, Dueland S, Ree AH. Individual tumor volume responses to short-course oxaliplatin-containing induction chemotherapy in locally advanced rectal cancer - Targeting the tumor for radiation sensitivity? Radiother Oncol 2016 Jun;119(3):505-11. Epub 2016 mar 8 **PMID:** 26968754

Dueland S, Ree AH, Grøholt KK, Saelen MG, Folkvord S, Hole Kh, Seierstad T, Larsen SG, Giercksky KE, Wiig JN, Boye K, Flatmark K. Oxaliplatin-containing Preoperative Therapy in Locally Advanced Rectal Cancer: Local Response, Toxicity and Long-term Outcome.Clin Oncol (R Coll Radiol) 2016 Aug;28(8):532-9. Epub 2016 feb 14 **PMID:** 26888115

Frøysnes IS, Larsen SG, Spasojevic M, Dueland S, Flatmark K. Complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastasis in Norway: Prognostic factors and oncologic outcome in a national patient cohort. J Surg Oncol 2016 Aug;114(2):222-7. Epub 2016 mai 12 **PMID:** 27173150

Frøysnes I, Andersson Y, **Larsen SG**, Davidson B, Øien J-MT, Olsen, KH, Giercksky K-E, Julsrud L, Fodstad Ø, Dueland S, Flatmark K. Novel treatment with intraperitoneal MOC31PE immunotoxin in colorectal peritoneal metastasis-result from the ImmunoPeCa phase I trial. Ann Surg Oncol. submitted 2016. In press. ASO-2017-01-0097.

G. Doktorgrader

- PhD-kandidat Olaf Sørensen. Eksperimentelle studier om HIPEC. (Veiledning).
- PhD-kandidat Ida Storaug Frøysnes. Bruk av immunotoxin ved HIPEC. (Veiledning).

H. Prosjekter

RAS/BRAF/MSI ved cytoreduktiv kirurgi og HIPEC Stein Gunnar Larsen, Oslo universitetssykehus HF, Halfdan Sørbye, Helse Bergen HF. Prosjektperiode: 2015 – 2017. Deltakende helseregion: HSØ; HV;HM;HN

Ovarialmetastaser ved peritoneal carcinomatose og pseudomyxoma peritonei Stein Gunnar Larsen, Oslo universitetssykehus HF Prosjektperiode: 2012 – 2018. Deltakende helseregion: HSØ

Cure4PMP* Kjersti Flatmark, Oslo universitetssykehus HF Prosjektperiode: 2015 – 2020 Deltakende helseregion: HSØ, internasjonalt

Sykehuskostnader ved cytoreduktiv kirurgi og HIPEC Stein Gunnar Larsen, Oslo universitetssykehus HF Prosjektperiode: 2015 – 2017 Deltakende helseregion: HSØ

Molekylære markører ved peritoneale metastaser Kjersti Flatmark, Oslo universitetssykehus HF Prosjektperiode: 2009 – 2020 Deltakende helseregion: HSØ

Eksperimentell behandling av peritoneal carcinomatose/pseudomyxoma peritonei Kjersti Flatmark, Oslo universitetssykehus HF Prosjektperiode: 2007 – 2018 Deltakende helseregion: HSØ

ImmunoPeCa-studien, tidlig utprøving av MOC31PE immuntoksin ved peritoneal carcinomatose Kjersti Flatmark, Oslo universitetssykehus HF Prosjektperiode: 2012 – 2017 Deltakende helseregion: HSØ

LARC-EX-studien, eksfolierte peritoneale tumorceller som biomarkør for utvikling av peritoneal carcinomatose Kjersti Flatmark, Oslo universitetssykehus HF Prosjektperiode: 2012 – 2017 Deltakende helseregion: HSØ

Helsedirektoratet

Helhetlig gjennomgang av nasjonale og flerregionale behandlingstjenester i spesialisthelsetjenesten 2017

Spørsmål til tjenestens faglige referansegruppe

SETT MARKØREN I DET GRÅ FELTET FØR DU STARTER SKRIVINGEN.

Navn på tjenesten:	Hyperterm intraperitoneal kjemoterapi (HIPEC)
Lokalisering:	Radiumhospitalet

1. Hvor ofte arrangeres det møter mellom tjenesten og referansegruppen?

   Informelle møter på NGICG 2-3 ganger per år

2. Deltar den faglige referansegruppen i utarbeidelse av tjenestens årsrapport?

   Nei

3. Har referansegruppen bidratt i utarbeidelse av henvisningskriterier og henvisningsrutiner?

   Ja

4. Har referansegruppen bidratt i utarbeidelse av informasjon om tjenesten til helsepersonell og brukere av tjenesten?

   Nei

5. Mandat for faglige referansegrupper forutsetter at det enkelte medlem skal overvåke om tjenesten drives etter intensjonen, når det gjelder å gi et klinisk tilbud til pasienter fra egen region. Har referansegruppens medlemmer etablert rutiner for tilbakemelding til eget RHF?

   Nei

6. Har tjenesten etablert et system for å ivareta brukermedvirkning?

   Nei

Tilleggsinformasjon

7. Dersom du har informasjon som er viktig for å forstå hvordan tjenesten fungerer som en nasjonal eller flerregional behandlingstjeneste, så kan dette beskrives her:

191216 arl