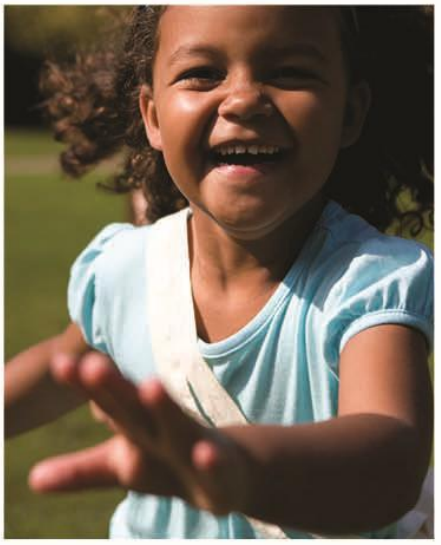
NHS Commissioning Board

Clinical Commissioning Policy: Cytoreduction surgery for patients with peritoneal carcinomatosis



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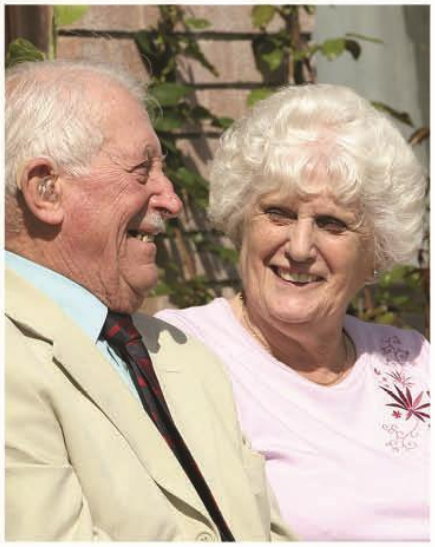

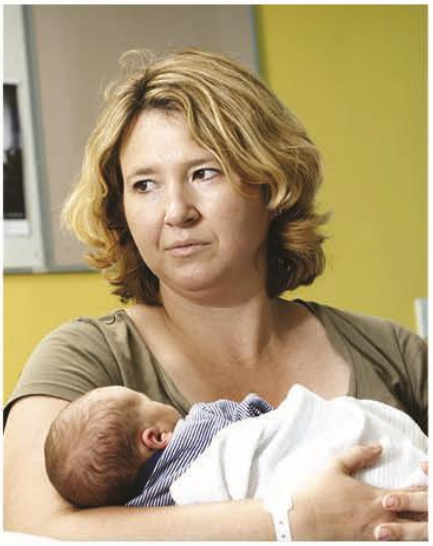

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NHS Commissioning Board

Clinical Commissioning Policy for Cytoreduction surgery for patients with peritoneal carcinomatosis

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Specialised Colorectal Services

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Contents

Policy Statement

This policy outlines the commissioning policy of the NHS Commissioning Board in relation to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis secondary to colorectal carcinoma, gastric carcinoma, pancreatic carcinoma and ovarian carcinoma.

In creating this policy the NHS CB has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

The NHS CB has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012.The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary

Peritoneal carcinomatosis is an advanced form of cancer found in the peritoneal cavity; the fluid-filled gap between the walls of the abdomen and the organs in the abdomen. This type of cancer occurs when cancers spread from their origin in, for example, the appendix, bowel, rectum or ovaries. It is associated with short survival and poor quality of life, and may lead to bowel obstruction, accumulation of fluid in the peritoneal cavity and pain.

Cytoreductive surgery refers to the removal or destruction of all visible tumors present throughout the abdomen. Combined with hyperthermic (warmed) intraperitoneal chemotherapy this aims to provide curative treatment.

For colorectal cancer there is a clear long term survival benefit for selected patients. For ovarian, gastric and pancreatic cancers the scientific evidence is equivocal or lacking.

Information on the outcome of treatments for these patients will be collected and considered when this policy is reviewed.

1. Introduction

Peritoneal carcinomatosis is an advanced form of cancer found in the peritoneal cavity. This type of cancer occurs when cancers spread from their origin in, for example, the appendix, bowel, rectum or ovaries. It is associated with short survival and poor quality of life, and may lead to bowel obstruction, accumulation of fluid in the peritoneal cavity and pain.[1]

Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy aims to provide curative treatment through complete removal of the tumour.

For the purpose of this policy the term cytoreduction surgery refers to the surgical cytoreduction procedure followed by hyperthermic intraperitoneal chemotherapy (CRS + HIPEC).

The following are covered by this policy

- Peritoneal carcinomatosis secondary to colorectal carcinoma, gastric carcinoma, pancreatic carcinoma and ovarian carcinoma

The following are not in the scope for this policy

- Pseudomyxoma peritonei, peritoneal mesothelioma, primary peritoneal carcinoma or peritoneal or abdominal sarcomatosis

2. Definitions

Peritoneal cavity is the space between the two membranes that separate the organs in the abdomen from the abdominal wall.

Peritoneal carcinomatosis is traditionally regarded as an 'end stage' feature of abdominal cancers and median survival rates of 6 months or less are identified in the literature.[2,3,4]

Cytoreduction surgery followed by hyperthermic intraperitoneal chemotherapy has developed as a treatment for patients with peritoneal carcinomatosis during the last 20 years.[5,6] The procedure involves removal of the maximum amount of the visible (macroscopic) tumour through a series of peritonectomy procedures (greater and lesser omentectomies, right and left upper quadrant peritonectomies, and anterior parietal and pelvic peritonectomies) with resection of involved nonessential organs as required. The exact scope of the surgery is dependent on the spread of the visible tumour in each patient.[1,7]

Hyperthermic intraperitoneal chemotherapy involves flushing the abdominal cavity with a chemotherapy agent. This can be performed either as an open or closed procedure. The therapeutic aim is to achieve a high local concentration of chemotherapy in the peritoneal cavity and absorption of the substance into the superficial cell layers and therefore cause only minimal systemic toxic side effects from the cytostatic medication. Heating the chemotherapy agent increases its therapeutic effect by improving penetration of the tissue.[1,8]

3. Aim and Objectives

This policy addresses cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis secondary to colorectal carcinoma, gastric carcinoma, pancreatic carcinoma and ovarian carcinoma. The aim of the treatment is to provide complete cytoreduction and cure.

It does not concern the use of this technique for pseudomyxoma peritonei which is the subject of a separate policy.

4. Criteria for commissioning

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy will be commissioned for patients with peritoneal carcinomatosis secondary to colorectal cancer. It will not be commissioned when metastatic disease is more extensive than the peritoneum alone. 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
- Malignant peritoneal mesothelioma
- Peritoneal carcinomatosis of non-colorectal origin

5. Patient pathway

Patients will be referred by secondary care consultants in accordance with the service specification and be discharged back to their care.

The following two Trusts are able to provide this service under this policy:

- The Christie NHS Foundation Trust
- Basingstoke and North Hampshire NHS Foundation Trust

6. Governance arrangements

A separate service specification has been developed for this service.

In accordance with NICE IPG 3319 the evidence on safety shows significant risks of morbidity and mortality, which need to be balanced against the perceived benefit for each patient. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

7. Epidemiology and needs assessment

	Rates	**Numbers**
Incidence of colorectal cancer in England (2010)	56.5/100,000 males 36.1/100,000 females	33,218 (actual)
Peritoneal Carcinomatosis secondary to colorectal cancer	7-10%	2325-3322
Peritoneal Carcinomatosis as sole site of metastasis	4.3[10]-4.8%[11]	1428-1594
No significant comorbidity and suitable for referral	50%[12]	714-797
Informed consent and fit for surgery	1:3 – 1:4[12]	178-266

8. Evidence Base

Evidence of effectiveness
It cannot be assumed that peritoneal carcinomatosis of all origins can be considered together although this was position for the NICE IPG evidence review.[1]

To address this issue the key grade 1 evidence specific to peritoneal carcinomatosis of colorectal origin that was considered for the NICE guidance (randomised control trial[13] and systematic review with meta-analysis[2]) will be considered in addition to the more recent evidence for this review.

There is also a general finding with regard to surgical expertise and completeness of cytoreduction, which will be covered at the end of this section.

Colorectal Carcinoma
The literature search revealed 2 very similar cohort studies that appeared in different journals by the same authors, with different lead authors[14,15], the earlier paper[14] considers only the outcomes of those patients with disease of colorectal origin. Only this earlier paper is therefore considered here.

The review of the literature also yielded 2 randomised controlled trials each comparing different hyperthermic intraperitoneal chemotherapeutic agents.[16,17] Neither of these addressed the question of this review. Also found were a number of studies including a consecutive case-series[18], case-series[19], and case-series from registries[20,21], the results of which are in accord with the other studies and do not add additional information relevant to the purpose of this review. These will not be discussed further in this review.

One trial registration filing[22] for a randomised control trial comparing cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy to standard care was identified. This trial is not expected to report until 2017.

The international consensus statement on peritoneal carcinomatosis produced by representatives from Germany, Netherlands, USA, Italy, Japan, Spain, Australia, France and Israel[36] describes a ‘paradigm change’ away from a fatalistic approach toward a potentially curative approach using cytoreduction surgery and hyperthermic intraperitoneal chemotherapy as being ‘justified by the current state of the international data’. Specifically they note the high quality randomised controlled trial (evidence grade 1b) that shows a clear survival benefit.[13,50]

In an intention to treat analysis in August 2007, after a median follow-up of 94 months, patients in the standard arm had a median survival of 12.6 months compared to the median survival of patients in the experimental arm of 22.2 months (p=0.028). The 6-year survival was 5% in the standard arm and 20% in the experimental arm.

The meta-analysis by Cao et al.[2] showed little difference between cytoreduction and early postoperative intraperitoneal chemotherapy. It only included the first three

years of the Verwaal [50] study where much clearer benefits are shown in the longer term data.[13] These longer term data show a five-year survival of 45%. Criteria for entry to the trial were under age under 71 years and fit for major abdominal surgery.

Compared, indirectly, with the five-year stage-specific relative survival rates for ovarian cancer from the Anglia Cancer Network for the period 2004-2008 survival is improved. In this registry for adults (15-99 years) the more usual five-year survival for patient with peritoneal carcinomatosis would be between 6% (stage IV disease) and 22% (Stage III disease).[51] A large multicentre cohort[14] also showed five-year survival of 27% (evidence grade 2b).

Gastric Carcinoma

Since the NICE review[1] of cytoreduction surgery there has been randomised control trials published of its use in peritoneal carcinomatosis secondary to gastric carcinoma. However the randomised controlled trials[23,24] only considered the additional benefits of hyperthermic intraperitoneal chemotherapy when added to cytoreduction surgery. These trials showed positive benefits to the combination of cytoreduction surgery and hyperthermic intraperitoneal chemotherapy compared to cytoreduction surgery alone, in keeping with the retrospective multi-centre cohort series.[25]

These studies do not consider the primary question of the effects of cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy compared to systemic chemotherapy. However, they do provide evidence that there are additional benefits of hyperthermic intraperitoneal chemotherapy when used with cytoreduction surgery in peritoneal carcinomatosis secondary to gastric carcinoma. There is also clear evidence of the survival benefits with improving completeness of the cytoreduction procedure.[15,23,25,52.53]

Pancreatic Carcinoma

Cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy is not currently used in the treatment of peritoneal carcinomatosis secondary to pancreatic carcinoma.[26] So it is not possible to address the primary question of the effects of cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy compared to systemic chemotherapy from the current literature.

Prognosis in this condition is extremely poor[26] and it would be inappropriate to extrapolate from the evidence from other cancers causing peritoneal carcinomatosis.

Ovarian Carcinoma

The review of the literature found 3 reviews [27,28,29] (one randomised trial of chemotherapy versus primary surgery (EORTC-NCIC)[30], and one trial that replicated the protocol of the EORTC-NCIC randomised trial.[31]

Also found were: one retrospective case-control study of cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreduction surgery[32], one

retrospective case series[33], one large consecutive-case series[34] and one non-randomised phase II efficacy trial of cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy.[35]

Two of the systematic reviews [28,54] identified only low quality evidence[55] in the form of retrospective studies with significant risk in their design of bias. The third systematic review found much higher quality evidence but comparing systematic chemotherapy with a range of regimes using intraperitoneal chemotherapy at some point in their care pathway.[27] The meta-analysis with this review showed a clear benefit of treatment regimes that included intraperitoneal chemotherapy.

The randomised trial of chemotherapy versus primary surgery by Vergote et al.[30] showed no difference between chemotherapy and cytoreduction surgery HR 0.98 (90% confidence interval [CI], 0.84 to 1.13). However this trial had a very low proportion of patients who had residual disease less than 1cm (41.6%) this is much lower than most trials in this area report, so applicability may be limited. Retrospective case analysis following the same protocol as this randomised trial[31] had 71% of patients with residual disease of less than 1cm, and a significant survival benefit in the uncontrolled treatment arm with median overall survival of 50 months.

This proportion of patients with complete cytoreduction is much more in keeping with that more generally published and given the strongly identified link between completeness of cytoreduction and survival this calls into question the generalisability of the results (no difference in outcomes between chemotherapy and cytoreduction surgery) made by Vergote et al.[30] Success rates appear to depend on careful patient selection.

Outcomes and expertise

There was a clear theme within all the available literature relating to what might loosely be called 'expertise'. The cytoreduction surgery places heavy demand on the surgical team[36] with the operations lasting 8-12 hours [7,37,38] and requiring a meticulous approach. There is a clearly described learning curve in performing these procedures.[8,39,40]

A prognostic factor repeatedly reported across the literature for peritoneal carcinomatosis secondary to colorectal, ovarian and gastric carcinomas, is completeness of cytoreduction.[7,8,14,15,25,41-49]. So if we can take completeness of cytoreduction as a marker of surgical technique then there is a clear correlation between surgical technique and outcome. Institutional experience is specifically noted as an important factor in toxicity and being an independent prognostic factor.[15]

This is an important policy consideration that has not yet come to prominence in the reviews of the evidence. It is a consideration of particular importance in the interpretation of the randomised trial of chemotherapy versus primary surgery in ovarian carcinoma (EORTC-NCIC)[30], as is clearly shown by the trial that replicated its protocol.[31]

Evidence of cost effectiveness
No cost or cost effectiveness studies were identified by the review for this policy.

Safety
This review has limited its consideration of the literature that reports the safety characteristics of cytoreduction surgery and hyperthermic intraperitoneal chemotherapy, because the literature is moderately consistent across disease origin, type of study, and time. It is also not straight-forward to control for the effect of 'expertise' or completeness from the data presented in the literature.
The 11 papers reporting safety characteristics identified cover colorectal, gastric, and ovarian carcinomas and include all the most recent paper reporting morbidity.[14,23,34,35,41,56-61]

In general 30-day mortality is less than 5% with some trial and series showing 0% 30-day mortality. Major complications occurred at between 15% and 40% (and might commonly include paralytic ileus and more rarely some of the following pneumonia, pancreatitis, pneumothorax, intra-abdominal abscess, renal insufficiency, urine bladder dysfunction, wound infection, pleural effusion, thrombosis, cardiac arrhythmia, pulmonary embolism, and re-operation).

These are generally in line with other major abdominal operations.

Summary of findings from the evidence review for this policy

Clinical Effectiveness

- When delivered by surgeon and units with the experience and expertise in achieving high rates of complete cytoreduction provides a significant survival benefit in peritoneal carcinomatosis secondary to colorectal and ovarian carcinoma.
- Cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy is more effective than cytoreduction surgery alone in gastric carcinoma, but the literature has not yet explored its specific benefit over systemic chemotherapy.
- The evidence suggests that the completeness of cytoreduction is an important determinant of effectiveness, and therefore this parameter should be monitored where the procedure is undertaken.
- No studies of cytoreduction surgery for people with carcinoma of the pancreas were identified.

Cost/cost effectiveness

- No studies of cost or cost effectiveness were identified.

Safety

- Cytoreduction surgery and hyperthermic intraperitoneal chemotherapy is of equivalent safety to other major abdominal procedures. But it is important to consider the evidence for cytoreduction surgery and hyperthermic

intraperitoneal chemotherapy separately for peritoneal carcinomatosis from each of colorectal, gastric, pancreatic and ovarian carcinoma.

Equity issues
There are no articles identified that specifically address equity issues.

9. Rationale behind the policy statement

Peritoneal carcinomatosis arises from the spread of different sorts of abdominal cancers. For colorectal cancer there is a clear long term survival benefit for selected patients. For ovarian, gastric and pancreatic cancers the evidence is equivocal or lacking.

10. Mechanism for funding

Through the responsible area team.

11. Audit Requirements

This procedure should meet the requirements of NICE IPG 331 and audit data shared with service commissioners. Audits should include the completeness of cytoreduction.

12. Documents which have informed this policy

Solutions for Public Health (SPH), and Bazian. Cytoreduction Surgery For Peritoneal Carcinomatosis. Evidence review Commissioned by the National Specialised Services Transition Team (NSSTT) in England. September 2012.

NICE. Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. IPG331. London: National Institute for Health and Clinical Excellence, 2010

The Christie NHS Foundation Trust. Referral Criteria for Peritoneal Tumours to the Peritoneal Tumour Service.

13. Links to other policies

The mechanism operated by the NHS CB for funding requests outside of the clinical criteria in this policy is yet to be finalised.

14. Date of Review

April 2014

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Change Notice for Published Specifications and Products

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Amendment **to the Published Products**

Product Name	Cytoreductive surgery for patients with peritoneal carcinomatosis
Ref No	A08/P/a
CRG Lead	Specialised Colorectal Services

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
Cytoreductive surgery for peritoneal carcinomatosis	Cytoreductive surgery for patients with peritoneal carcinomatosis	Front and title page	To standardise naming and coding of products	Programme of Care Director for Internal Medicine	September 2013