NHS England

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Clinical Commissioning Policy: Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Mesothelioma

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NHS England Clinical Commissioning Policy: Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Mesothelioma

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Contents

Policy Statement

NHS England will not routinely commission cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy for peritoneal mesothelioma because there is inadequate evidence for its clinical and cost-effectiveness.

In creating this policy NHS England 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

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

Peritoneal mesothelioma is a form of cancer affecting the lining of the stomach (the peritoneum). It is caused by the ingestion of asbestos fibers and has a rapid and fatal course. This is because the early symptoms of peritoneal mesothelioma are similar to those of other gastrointestinal illnesses. As a result, diagnosis is often delayed and occurs at an advanced stage of disease (when it has spread throughout the stomach). If left untreated, survival rarely exceeds a year.

Cytoreduction surgery (CRS), also referred to as ‘de-bulking’ surgery, aims to remove as much of the tumour as possible. When the technique is used in patients with peritoneal mesothelioma, the surgery involves many surgical procedures and treatment can take a long time.

The surgery can also be carried out along with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) treatment. HIPEC is used in patients who have cancers of the abdomen. This involves using a high dose of chemotherapy which aims to kill any remaining cancer cells left after a cytoreduction surgery. HIPEC is a heated and sterilized chemotherapy treatment.

1. Introduction

Background

Mesothelioma is a rare, usually aggressive, form of cancer that principally affects the serosal surfaces of the pleura (70%), peritoneum (30%) and, in a small proportion of cases, the tunica vaginalis of the testis or pericardium (1-2%). It is strongly associated with exposure to asbestos.

Peritoneal mesothelioma (also referred to as malignant peritoneal mesothelioma, peritoneal malignant mesothelioma, malignant primary peritoneal mesothelioma and abdominal mesothelioma) usually has a rapidly fatal course. Because the early symptoms may mimic those of a benign ailment of the gastrointestinal tract, diagnosis is often delayed, occurring at an advanced stage of disease when it has spread throughout the peritoneal cavity. If left untreated, survival rarely exceeds a year.

There are three main histological types of malignant peritoneal mesothelioma: epitheliod, sarcomatoid and biphasic (or mixed). Epitheliod mesothelioma is the most common type – seen in around 75-80% of patients; the biphasic subtype shows a mixture of both epitheloid and sarcomatoid features and is seen in about 20-25% of patients. The pure sarcomatoid subtype is rare. Distinction between these morphologic subtypes is important because patients with pure epithelial mesotheliomas have a better prognosis than do those with sarcomatous or mixed/biphasic tumours (Levy et al. 2008). Tumours can also be classified according to whether they are diffuse or localized, which gives rise to different clinical presentations.

Patients with diffuse peritoneal malignant mesotheliomas commonly experience abdominal pain, abdominal distension or ascites, nausea, anorexia, and weight loss. Gastrointestinal complications such as bowel and renal obstruction may occur with advanced disease. Patients with localized peritoneal malignant mesotheliomas may complain of localized abdominal pain or a palpable abdominal or pelvic mass. Symptoms can be very severe and difficult to manage clinically. Prognosis is generally better with localised than with diffuse tumours (Levy et al. 2008).

Other rarer varieties of mesothelial neoplasm affecting the peritoneum include benign adenomatoid tumour and tumours on the borderline between benign and malignant such as well-differentiated papillary mesothelioma and multicystic mesothelioma, both of which commonly arise from the pelvic surfaces of the peritoneum and mostly occur in women. Well-differentiated papillary mesothelioma is rare and has no reported link with exposure to asbestos. The tumour is often discovered incidentally during pelvic examination or surgery. It has a good prognosis and is either cured with complete surgical resection or follows an indolent course with long survival. Multicystic mesothelioma (also referred to as peritoneal inclusion cyst, multilocular inclusion cyst, and benign multicystic mesothelioma) is an unusual, multilocular cystic tumour. It is thought to develop as a result of peritoneal reactive proliferation secondary to previous intra-abdominal surgery, infection, trauma or endometriosis (Chua, et al. 2011). It follows a benign or indolent course in most patients, but can recur locally and, in rare cases, may show malignant transformation (Levy et al. 2008).

The clinical presentation and radiological findings (CT, US and MRI) of peritoneal

mesothelioma can often mimic those of psuedomyxoma peritonei, and histological analysis may not be available until after surgery, or may be equivocal

Treatment
Treatment options for peritoneal mesothelioma were previously limited to systemic chemotherapy, palliative (de-bulking) surgery, and palliative/supportive care including repeated paracentesis and drainage of ascites and, in a few patients, abdominal radiation. In practice relatively few patients undergo palliative surgical treatments, due to the nature and extent of the tumour and the technical expertise required in de-bulking.

More recently, treatment of peritoneal surface malignancies has evolved to include the more aggressive combination of cytoreductive surgery and peri-operative intra-peritoneal chemotherapy. This combined technique was first developed in the 1980s by Paul Sugarbaker at the Washington Cancer Institute, USA, with the intention of providing a curative treatment for peritoneal surface malignancies. In most cases this radical procedure is not appropriate, and careful patient selection is important.

Cytoreduction surgery (CRS) (also referred to as *cytoreductive surgery*) is performed under general anaesthetic via laparotomy. The aim of CRS is to remove all visible (macroscopic) tumour. The scope of surgery will depend on the spread of visible tumour in each case. When used in patients with peritoneal mesothelioma, the surgery involves up to six peritonectomy procedures (greater and lesser omentectomies, right and left upper quadrant peritonectomies, and anterior parietal and pelvic peritonectomies) together with resection of involved non-essential organs as required.

Whilst the aim of CRS is to remove all macroscopic tumour, microscopic and residual macroscopic tumour may be left behind. To treat any residual tumour, on completion of the CRS, the abdomen is perfused with chemotherapy solution, heated to between 40 and 43°C for 60 to 120 minutes, which is then drained from the abdomen prior to closure. Intraoperative intraperitoneal administration of chemotherapy (usually referred to as hyperthermic intraperitoneal chemotherapy or HIPEC) allows the drug to be distributed uniformly to all surfaces of the abdomen and pelvis. Heating the perfusion fluid is thought to increase its therapeutic effect by increasing drug penetration and the cytotoxic effect of the drugs used. A further course of systemic or intraperitoneal chemotherapy, referred to as early postoperative intraperitoneal chemotherapy (EPIC), may be administered at normal temperature, for up to five days following surgery. Different centres vary in the surgical technique they use (whether closed, open or semi-closed) and in the chemotherapy protocols (in terms of technique, drugs used, carriers, timing and temperature).

2. Definitions

Peritoneum or **peritoneal membrane** is the continuous connective tissue membrane that covers the walls of the abdominal cavity, and the organs within it.

Peritoneal cavity is the space within the continuous membrane (peritoneum) that covers the walls of the abdominal cavity and the organs within it.

Peritoneal Mesothelioma (also referred to as malignant peritoneal mesothelioma, peritoneal malignant mesothelioma, malignant primary peritoneal mesothelioma and abdominal mesothelioma is a rare, usually aggressive, form of cancer affecting the serosal (inner) surface of the peritoneum

Peritonectomy is the surgical removal of areas of the peritoneum.

Cytoreduction surgery (CRS) involves removal of the maximum amount of the visible (macroscopic) tumour through a series of peritonectomy procedures, and removal or resection of involved non-essential organs as required. The exact scope of the surgery is dependent on the spread of the visible tumour in each patient.

Hyperthermic intraperitoneal chemotherapy involves flushing the abdominal cavity with a chemotherapy agent. This can be performed either as an open (intra-operative) or closed procedure. The therapeutic aim is to achieve a high local concentration of chemotherapy in the peritoneal cavity in order to kill any residual tumour cells. Heating the chemotherapy agent increases its therapeutic effect by improving penetration of the tissue.

3. Aim and objectives

The aim of this policy is to set out the commissioning policy of NHS England with respect to cytoreductive surgery and hyperthermic peritoneal chemotherapy.

The objectives are to:

- Summarise the published evidence pertaining to the clinical and cost-effectiveness of CRS in peritoneal mesothelioma and its clinical sub-groups.
- Explain the rationale for the NHS England commissioning position.

4. Epidemiology and needs assessment

Mesothelioma has a strong association with exposure to asbestos. In men, asbestos exposure has been shown to be the cause in 90% of pleural malignant mesotheliomas and 60% of peritoneal malignant mesotheliomas (Chua et al. 2009). Peritoneal malignant mesothelioma usually develops in individuals exposed to higher levels of asbestos. In women, asbestos exposure plays a smaller role in the development of malignant mesothelioma; less than a quarter of women who develop peritoneal malignant mesothelioma have been exposed to asbestos (Levy et al. 2008). Other aetiological factors implicated in the development of malignant mesothelioma include exposure to therapeutic irradiation, erionite (a mineral fibre found in Turkey), simian virus 40 and, rarely, chronic pleural or peritoneal irritation. Malignant mesothelioma occasionally occurs in young patients with no exposure history. Most malignant mesotheliomas occur in men, with a median age at presentation of 60 years. In women, peritoneal malignant mesothelioma occurs in a slightly younger age group (mean age, 50 years) and, in general, has a better prognosis.

Incidence

Peritoneal mesothelioma was once extremely rare but has shown an increasing incidence worldwide following the vast mining of asbestos, which peaked in the 1970s (Chua et al. 2009). In 2009, the number of reported new diagnoses of peritoneal mesothelioma in England, based on cancer registry data, was 2209 (1832 men, 377 women), equivalent to an age-standardised annual incidence of 9.29 per 100,000 population for men and 1.54 per 100,000 population for women (Public Health England, 2014).

Mortality
In 2011, there were almost 2,300 deaths from mesothelioma (including peritoneal mesothelioma) of which around 85% were in men, and 15% in women. Based on the latest projections, the annual number of deaths from mesothelioma in the UK is expected to continue to rise in future years before peaking at around 2,500 per year towards the end of this decade. Most deaths occurring now are a consequence of the long latency period (i.e. the time between initial exposure to asbestos and symptom onset) which is typically between 20 and 30 years for peritoneal mesothelioma, and somewhat shorter than the latency period for pleural mesothelioma of 30–40 years (Boffetta, 2007).

Survival
The median survival of untreated malignant peritoneal mesothelioma is reported to be around 6 months (Turner et al. 2012). Treatment with palliative surgery and/or systemic/intraperitoneal chemotherapy is associated with a median survival of around 12 months to two years (Baratti et al. 2013, Baratti et al. 2011). Biphasic/sarcomatoid histology, lymph-node involvement, and diffuse tumours, as opposed to localized, are reported to be associated with a poorer prognosis (Baratti et al. 2013). Women appear to have a more favourable prognosis than men. Suggested reasons for this difference include differing aetiology and causative factors, differing histology, and earlier presentation of the disease amongst women (Yan et al. 2007).

Activity and cost
Between 1998 and October 2013, 44 patients with peritoneal mesothelioma underwent the procedure, with approximate average referrals of 5 cases per year. The rate of referrals to the service is reported to have increased recently, and this has resulted in an increase of surgical intervention to around 6-8 cases per year.

This activity is currently funded through Individual Funding Requests (IFR), and based on an expected average of 8 cases per year, the total cost of CRS plus HIPEC for patients with peritoneal mesothelioma in England, at a cost per case of £57k, is estimated as £456k per year.

5. Evidence base

Clinical effectiveness
The review found one well-conducted systematic review of prospective non-randomised uncontrolled observational studies, two more recently published retrospective uncontrolled observational studies, and one ongoing study of CRS plus HIPEC in patients with malignant peritoneal mesothelioma. Median overall

survival in the systematic review studies ranged from 29.5 to 92 months; median survival in the two more recently published studies was within the same range (38.4 and 63.2 months). In one small retrospective uncontrolled observational study of 26 patients with multicystic peritoneal mesothelioma receiving the intervention, median follow up was 54 months; all patients were still alive at the time of the study.

A NICE overview of studies investigating the use of CRS and HIPEC in peritoneal carcinomatosis included one uncontrolled case series for which median survival was reported as 27.1 months for the 27 patients with peritoneal mesothelioma as the primary tumour of origin. A second more recently published retrospective uncontrolled cohort study was found which reported median survival of 41 months for 88 patients with peritoneal carcinomatosis arising from peritoneal mesothelioma.

Since all of the studies identified in this report were uncontrolled case series, their findings are of very limited value in determining the clinical effectiveness of the intervention in the treatment of either localized or diffuse peritoneal mesothelioma. The patients included in these studies were those deemed clinical suitable for radical surgery, and therefore not representative of all patients with the condition. These limitations mean that no clear conclusions can be drawn as to the magnitude of any survival advantage associated with the procedure.

Cost-effectiveness
The review identified one cost-effectiveness study of CRS plus HIPEC in the treatment of 136 patients with peritoneal carcinomatosis, 15 of whom had peritoneal mesothelioma as the primary tumour. For patients with peritoneal mesothelioma as the primary tumour of origin, median survival was 49 months, average health care costs per patient were 55,062 Australian dollars (range 23,261 to 94,104), equivalent to around £30k (range £13k to £53k) and average cost per life year gained was 20,521 Australian dollars, equivalent to around £11.5k. Although the study considered key health care costs associated with the intervention, its findings were based on a very small sample of patients with peritoneal mesothelioma with advanced disease in the form of peritoneal carcinomatosis. There was no comparator group receiving standard treatment against which costs and survival outcomes of the intervention could be compared, there was no sensitivity analysis around the estimated cost per life year gained, and transferability of results to the NHS is difficult to assess.

Safety
In the systematic review of CRS plus HIPEC in patients with all-type or diffuse malignant peritoneal mesothelioma, overall operative mortality was 3.1% (ranging from 0 to 10.5% in individual case series). Morbidity ranged from 20 to 41% and re-operation rates from 4 to 42%. Median and mean lengths of hospital stay ranged from 7 to 33 days and 24 to 41.5 days respectively.

6. Rationale behind the policy statement

There is **insufficient evidence** to support routine commissioning of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for peritoneal mesothelioma, based on the current published research.

7. Criteria for commissioning

Not applicable.

8. Patient pathway

Not applicable.

9. Governance arrangements

Not applicable.

10. Mechanism for funding

CRS will not routinely be funded for peritoneal mesothelioma.

11. Audit requirements

Not applicable.

12. Documents which have informed this policy

Cytoreductive surgery in the treatment of peritoneal mesothelioma. 2014: Solutions for Public Health (Greater East Midlands Commissioning Support Unit). www.sph.nhs.uk

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

This policy will be reviewed in 2016/17, unless information is received which indicates that the proposed review date should be brought forward or delayed.

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Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
1	Whole document	First draft	June 2014	SN
2	Whole document	Placed in new template	Sept 2014	NMc
3	Plain Language Summary	Addition of text / final edit	Sept 2014	NMc
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