

# **Clinical Commissioning Policy: Gemcitabine and capecitabine following surgery for pancreatic cancer (all ages)**

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**Additional Circulation List**

<b>Description</b>	Routinely Commissioned - NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
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**Cross Reference****Superseded Docs**  
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# **Clinical Commissioning Policy: Gemcitabine and capecitabine following surgery for pancreatic cancer (all ages)**

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Chemotherapy**

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## Policy Statement

NHS England will commission gemcitabine and capecitabine following surgery for pancreatic cancer in accordance with the criteria outlined in this document.

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

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need 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 under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

## Plain Language Summary

### About pancreatic cancer

The pancreas is part of the digestive system and is a large gland in the body that produces digestive juices, insulin and other hormones to do with digestion. Around

9,600 people in the United Kingdom (UK) are diagnosed with pancreatic cancer each year and it is the eleventh most common cancer (Cancer Research UK, 2018). It is more common in older adults and almost half of all new cases are diagnosed in people aged 75 and over (Cancer Research UK, 2018). In the past 10 years, pancreatic cancer rates have increased and this trend is expected to continue over the next decade (Cancer Research UK, 2018).

When pancreatic cancer is detected at an early stage, there is a much greater chance that it can be cured with surgery, which is also referred to as a 'resection'. However, only about 10% of people with pancreatic cancer have potentially curative surgery because most pancreatic cancers have spread too far at the point of diagnosis to enable surgery to be effective. A pathologist will examine and grade the cancerous tumour that has been removed to help guide further treatment options.

This policy relates to cases of pancreatic cancer where, following surgical resection, a pathologist has determined that there are no remaining cancer cells visible to the naked eye. This is termed microscopic clearance or microscopic infiltration of the resection margin and is graded by the pathologist as either 'R0' or 'R1'.

### **About current treatments**

The current treatment options for pancreatic cancer include surgery, radiotherapy and chemotherapy. Treatment options depend on several factors, including the type and stage of cancer (a way of describing where the cancer is located, if or where it has spread, and whether it is affecting other parts of the body), possible side effects, overall health and individual preference.

Surgery for pancreatic cancer may be combined with radiation therapy and / or chemotherapy to reduce the chances of the cancer returning; if given after surgery, this is called adjuvant therapy. In England, currently gemcitabine is given alone as an adjuvant chemotherapy treatment for people that have undergone potentially curative surgery for pancreatic cancer and who do not have any remaining cancer cells visible to the naked eye (R0 and R1). It is usually started within three months of surgery and continued for six months.

## **About the new treatment**

The new treatment combines a chemotherapy medicine called capecitabine with gemcitabine which is currently available. This combination is intended to further improve outcomes compared to gemcitabine alone. Both medicines are given at the same time and both work by stopping cells making and repairing DNA, which they need to grow and multiply.

## **What we have decided**

NHS England has carefully reviewed the evidence to treat resected pancreatic cancer, where either microscopic clearance (R0) or microscopic infiltration (R1) of the margins has been achieved, with adjuvant gemcitabine and capecitabine, and has concluded that there is enough evidence to make the treatment available.

## 1 Introduction

Pancreatic cancer is cancer that starts in the pancreas, a large gland in the body that produces digestive juices, insulin and other hormones to do with digestion. The majority of pancreatic cancers start in the cells that produce digestive juices and are called exocrine pancreatic cancers. Less commonly, pancreatic cancers start in the cells that produce insulin and hormones and are known as endocrine pancreatic cancers. Pancreatic cancer can also start in other types of cells but this is rare.

The current treatment options for pancreatic cancer include surgery, radiation therapy and chemotherapy. Treatment options and recommendations depend on several factors, including the type and stage of cancer (a way of describing where the cancer is located, if or where it has spread, and whether it is affecting other parts of the body), possible side effects, and the patient's preferences and overall health.

When detected early (also called resectable or borderline resectable pancreatic cancer), pancreatic cancer has a much higher chance of being cured with surgery. However, only about 10% of people with pancreatic cancer are able to have potentially curative surgery because most pancreatic cancers have already spread too far at the point of diagnosis.

Surgery for pancreatic cancer may be combined with radiation therapy and / or chemotherapy to reduce the chances of the cancer returning; if given after surgery, this is called adjuvant therapy. Examination and grading of the resection margins by a pathologist after surgery helps to guide further treatment options. There are three classifications used: (i) R0 – microscopic tumour clearance; (ii) R1 – microscopic tumour infiltration; and (iii) R2 – macroscopic residual tumour.

In England, currently gemcitabine is given alone as an adjuvant chemotherapy treatment for patients who have undergone potentially curative surgery for pancreatic cancer. Gemcitabine belong to a family of drugs called antimetabolites. The drug works by stopping cells making and repairing DNA which they need to grow and multiply. Gemcitabine is usually started within three months of surgery and continued

for six months. Common side effects include neutropenia, anaemia, bruising and bleeding, feeling sick, loss of appetite and tiredness.

Capecitabine, which is not licensed to treat this indication, is another chemotherapy drug that can be given in combination with gemcitabine to improve outcomes further after surgery. The drug is given concurrently with gemcitabine and for the same treatment duration. It belongs to the same family of drugs as gemcitabine and acts in the same way, preventing cancerous cells from re-producing.

It is proposed to treat cases of surgically resected pancreatic cancer with gemcitabine and capecitabine, where either microscopic clearance (R0) or microscopic infiltration (R1) of the margins has been achieved with surgery.

## 2 Definitions

Adjuvant therapy – any therapy, such as chemotherapy or radiotherapy, given after initial treatment to suppress the cancer from returning.

Antimetabolites – a group of drugs that interfere with the normal dividing and functions of cells.

Cancer – abnormal cells that divide in an uncontrolled way.

Chemotherapy – a type of cancer treatment where medication is used to kill the cancer cells. Chemotherapy also affects healthy cells and this can cause side-effects, which will vary depending on the type of cell affected.

Pancreatic cancer – a cancer that starts in the pancreas. The pancreas is part of the digestive system and is a large gland that produces digestive juices, insulin and other hormones to do with digestion.

Radiotherapy – a treatment where radiation is used to kill cancer cells. There are many different ways radiotherapy can be given, but they all work in a similar way. They damage cancer cells and stop them from growing or spreading in the body.

Side-effects may occur and are caused by radiation affecting the surrounding healthy tissues. These will vary depending on the healthy tissue affected and amount of radiation received.

Resectable pancreatic cancer – is pancreatic cancer that has been diagnosed when it is at an early stage and is potentially curable with surgery.

R grading system – is used after surgery to guide further treatment. The removed cancer is examined and graded by a pathologist using the following system:

- R0 – microscopic tumour clearance;
- R1 – microscopic tumour infiltration; and
- R2 – macroscopic residual tumour.

Staging for pancreatic cancer – this describes the size of the cancer, where it is and whether it has spread. It is used to help guide treatment. Scans and other tests, such as biopsies, will give information about the staging.

Type of pancreatic cancer – this is the type of cell the pancreatic cancer started in. The majority of pancreatic cancers start in the cells that produce digestive juices and are called exocrine pancreatic cancers. Less commonly, pancreatic cancers start in the cells that produce insulin and hormones and are known as endocrine pancreatic cancers. Pancreatic cancer can also start in other types of cells but this is rare.

### **3 Aims and Objectives**

This policy considered gemcitabine and capecitabine combination chemotherapy following surgery for pancreatic cancer.

The objectives were to establish, via an evidence review the efficacy and safety of using gemcitabine and capecitabine combination chemotherapy compared with gemcitabine given alone following pancreatic cancer surgery.

## 4 Epidemiology and Needs Assessment

Around 9,600 people in the UK get pancreatic cancer each year and it is the 11th most common cancer. In the past 10 years, pancreatic cancer rates have increased and it is thought they will continue to increase over the next decade (Cancer Research UK, 2018).

Pancreatic cancer is more common in older people and almost half of all new cases are diagnosed in people aged 75 and over; pancreatic cancer is uncommon in people under 40 years old. It is more common in people living in poorer areas and it affects men and women equally. In the past 10 years, pancreatic cancer rates have increased and it is thought they will continue to increase over the next decade (Cancer Research UK, 2018).

Common risk factors for pancreatic cancer include smoking, obesity, consuming foods high in fat, heavy alcohol use, diabetes and chronic pancreatitis (an inflammation of the pancreas which can occur for a variety of reasons). It can also run in families and is associated with rare inherited conditions.

It is estimated that approximately 10% of patients with pancreatic cancer will have surgery (Pancreatic Cancer UK, 2015). In England, this equates to approximately 845 patients a year. All cases of surgically resected pancreatic cancer where microscopic clearance (R0) or microscopic infiltration (R1) of the resection margins has been achieved with surgery would be assessed to determine if gemcitabine and capecitabine is able to be given (i.e., ability to tolerate the chemotherapy).

Of the 845 people undergoing potentially curative surgery, it is estimated that approximately 50% will have either R0 or R1 margins and will therefore be eligible for treatment under the criteria within the policy. The remaining 50% of cases will have R2 margins and fall outside the scope of this policy.

## 5 Evidence Base

NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indication.

An evidence review assessed the clinical and cost-effectiveness of using gemcitabine and capecitabine in combination as adjuvant therapy following potentially curative surgery for pancreatic cancer compared with gemcitabine alone.

The evidence review was based on 1 open label randomised controlled trial which compared adjuvant treatment with gemcitabine plus capecitabine with gemcitabine alone in 730 people who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resections). The main outcome of the study was overall survival, defined as the time from randomisation until death from any cause. Relapse-free survival, which was defined as the minimum time from randomisation to date of local tumour recurrence, lymph node spread, distant metastases or death from any cause, was a secondary outcome. Participants in the study were followed-up for a median of 43.2 months. The study included people with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). Although the study was generally well-conducted, it was open label and participants and study investigators knew which treatment had been allocated, which is a source of bias. However, the primary outcome of overall survival is unlikely to be influenced by bias.

Compared with gemcitabine alone there was a statistically significant increase of 2.5 months in the median overall survival time with gemcitabine plus capecitabine. The median overall survival time was 25.5 months in the gemcitabine group compared with 28.0 months in the gemcitabine plus capecitabine group.

Gemcitabine plus capecitabine had a statistically significant treatment effect on overall survival in people who had negative resection margins (R0 resections). In people who had positive resection margins (R1 resections) gemcitabine plus capecitabine had no statistically significant treatment effect on overall survival. However, the study was powered for the primary outcome of overall survival for the whole group; while the analysis of the R0 and R1 resection subgroups was pre-specified, caution should be exercised when interpreting the results of these individual subgroups. In this study, positive resection margins (R1) were defined as any tumour cell within 1 millimetre of any surface of the specimen.

In people who had R0 resections, gemcitabine plus capecitabine increased median overall survival by 11.6 months compared with gemcitabine alone (from 27.9 months

to 39.5 months). In people who had R1 resections, there was a 0.7 month difference between the 2 treatment groups for median overall survival (23.0 months in the gemcitabine group compared with 23.7 months in the gemcitabine plus capecitabine group).

Compared with gemcitabine alone, estimated overall survival at 5 years was found to be 12.5% higher with gemcitabine plus capecitabine (16.3% compared with 28.8%). These results are only estimates as not all people still alive at the end of the study would have had 5 years of follow-up. The study ran for approximately 7.5 years but participants could be recruited to the study at any time during the first 6 years.

There was no statistically significant difference between gemcitabine plus capecitabine and gemcitabine alone for median relapse-free survival time. So although an increase in overall survival was seen, no difference was seen in how long it took for the pancreatic cancer to relapse or progress in the people who were still alive. The median relapse-free survival time was 13.1 months in the gemcitabine group compared with 13.9 months in the gemcitabine plus capecitabine group. Three-year relapse-free survival was 20.9% in the gemcitabine group compared with 23.8% in the gemcitabine plus capecitabine group and 5 year relapse-free survival was 11.9% in the gemcitabine group compared with 18.6% in the gemcitabine plus capecitabine group.

Fourteen percent of participants in the gemcitabine group and 22% of participants in the gemcitabine plus capecitabine group stopped treatment early due to side-effects. There was no statistical significant difference between gemcitabine plus capecitabine and gemcitabine alone for the percentage of participants who had at least 1 treatment-related serious adverse event (26% in the gemcitabine group compared with 24% in the gemcitabine plus capecitabine group), although the study did not report how it defined treatment-related serious adverse events.

Adverse events were graded according to the National Cancer Institute common toxicity criteria, version 4.03. This grades adverse events on a scale of 1 to 5 with 4 being the most serious adverse event and 5 being death. Grade 3–4 adverse events were reported by 54% of participants in the gemcitabine group compared with 63% of participants in the gemcitabine plus capecitabine group. There was a statistically significant higher percentage of participants who had grade 3–4 adverse events of

diarrhoea, neutropenia and hand-foot syndrome in the gemcitabine plus capecitabine group compared with the gemcitabine group. There was a statistically significant lower percentage of participants who had grade 3–4 adverse events of infection and other infestations (adverse event category not defined in the paper) in the gemcitabine plus capecitabine group compared with the gemcitabine group:

- Diarrhoea: 2% in the gemcitabine group compared with 5% in the gemcitabine plus capecitabine group
- Neutropenia: 24% in the gemcitabine group compared with 38% in the gemcitabine plus capecitabine group
- Hand-foot syndrome: No participants in the gemcitabine group compared with 7% in the gemcitabine plus capecitabine group
- Infections and other infestations: 7% in the gemcitabine group compared with 3% in the gemcitabine plus capecitabine group.

## 6 Criteria for Commissioning

Capecitabine with gemcitabine combination therapy should be considered as adjuvant treatment in cases of pancreatic cancer, where either microscopic clearance (R0) or microscopic infiltration (R1) of the margins has been achieved following surgical resection. Treatment should commence within 12 weeks of surgery and continue for six months.

When used to treat this indication, both drugs are given concurrently in the following way:

- Gemcitabine is administered intravenously. Each patient will receive six cycles of treatment, each cycle comprising 1000 mg/m<sup>2</sup> given intravenously once a week for three of every four weeks; and
- Capecitabine is given orally. Each patient will receive six cycles of treatment, each cycle comprising 1660 mg/m<sup>2</sup> given daily for twenty-one days followed by seven days' rest.

The decision to select the patient for adjuvant treatment with gemcitabine and capecitabine must be made by the hepatobiliary and pancreatic multi-disciplinary team and the patient. The first cycle must be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy. A decision to continue or stop treatment should be made by the multi-disciplinary team and the patient.

## **7 Patient Pathway**

The patient pathway in accessing this treatment will be through the hepatobiliary and pancreatic multi-disciplinary team. This reflects existing care pathway arrangements for patients with pancreatic cancer.

## **8 Governance Arrangements**

As capecitabine is not a licensed medicine for this indication, any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Providers will be expected to follow trust and Cancer Alliance policies for the safe prescribing and monitoring of off-label licensed medications including compliance with MHRA safety alerts. Prescribers need to also be aware of their responsibilities as specified in MHRA Drug Safety Update volume 10 issue, 12 July 2017:2.

## **9 Mechanism for Funding**

Gemcitabine and capecitabine will be funded by local specialised commissioning teams, through established chemotherapy funding arrangements.

## **10 Audit Requirements**

Systemic Anti-Cancer Treatment (SACT) dataset.

## **11 Documents Which Have Informed this Policy**

NHS England Evidence Review for Gemcitabine and capecitabine following surgery for pancreatic cancer.

## **12 Date of Review**

This document will be reviewed when information is received which indicates that the policy requires revision.

## References

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