# Considerations for treatment of pancreatic cancer within the United Kingdom during the COVID-19 pandemic

## 1. DOCUMENT OUTLINE

### 1.1. Date and version

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### 1.2. Authors and contributors (to guidance document and the linked RT guidance documents)

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### 1.3. Revision history

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## 2. DOCUMENT AIM

The aim of this document is to bring together expert opinion in order to provide guiding principles for the management of upper gastrointestinal (UGI) cancers in the United Kingdom (UK) during the COVID-19 pandemic. It is anticipated that this document will be updated as evidence emerges relating to the added risks for cancer patients imposed by COVID19, and as further information is gathered relating to National Health Service (NHS) capacity and constraints during the pandemic period. Priority has been on forming expert opinion around existing evidence where available.

## 2. GLOSSARY

BRPC: Bordeline Resectable Pancreatic Cancer
PDAC: pancreatic ductal adenocarcinoma
PPPD: Pylorus Preserving Pancreatico-duodenectomy
SBRT: Stereotactic Body Radiotherapy
CRT: Chemoradiotherapy
mFOLFIRINOX: modified FOLFIRINOX (5FU, Folinic Acid, Irinotecan, Oxaliplatin) chemotherapy regimen
TRG: tumour regression grade

## 3. RATIONALE

As of 18th March 2020, in excess of 200,000 people worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the coronavirus disease 2019 (COVID-19) pandemic(1). Almost 9000 have died from this disease in the four months following the first reported case in December 2019(1). In the United Kingdom (UK), the first cases were reported on 31st January 2020 and of 18th March 2020 there are 2626 cases and 103 confirmed deaths, though the undiagnosed burden of disease in the community is considered to be far greater(2). Common symptoms resulting from infection with SARS-CoV-2 include cough, shortness of breath and fever. However, a proportion of patients die from multiple organ dysfunction syndrome rather than respiratory failure(3).

The COVID-19 pandemic is of particular concern for the management of patients with cancer, who are immunosuppressed both because of the cancer and as a consequence of the anti-cancer treatment they receive, and who frequently have a number of comorbidities. In a prospective Chinese series of 1590 patients, 18 (1%) had cancer (compared with a population cancer prevalence of 0.29%)(4). Cancer was associated with more severe CT findings and a higher risk of severe COVID-19 disease. Whilst drawn from small numbers, it also appears that recent anti-cancer therapy confers

a higher risk of more severe COVID-19 disease. Amongst patients with cancer, older age was an additional risk factor for severe events, though the older age of the cancer cohort compared with the comparator non-cancer cohort may have overexaggerated the risks from cancer (5). Nevertheless, a further series suggests that patients with cancer are at greater risk of SARS-CoV-2 infection (6).

Given these factors and the increasing prevalence of SARS-CoV-2 in the UK community, there are significant concerns about the impact of COVID-19 on patients with cancer. Of added concern is an expected surge in the number of cases that will threaten intensive treatment unit (ITU) bed availability, and that will reduce numbers of frontline clinical staff. Together, these factors mandate re-consideration of treatment pathways for patients with malignancies, including upper GI cancers, in order to account for both service constraints and the increased risks of SARS-CoV-2 infection; i.e. to limit service use whilst directing resources to achieve maximum benefit and to mitigate risks of infection with SARS-CoV-2, such as by avoiding hospital admission or attendance. However, there is very limited data to guide clinicians in adapting their treatment. The following considerations therefore represent the best expert consensus to support the UK upper GI community.

## 4. CONSIDERATIONS BY TREATMENT CONTEXT IN PANCREATIC CANCERS (PDAC)

### *4.1 RESECTABLE/BORDERLINE RESECTABLE TUMOURS (BRPC)*

#### 4.1.1. Upfront surgery and Neo-adjuvant therapy

There is concern that due to the expected increase in ITU bed occupancy rates during the COVID-19 pandemic, elective surgery may become a less viable option over the coming weeks to months. For patients in the system who are planned to undergo Whipple's procedure prior to the expected peak in ITU occupancy, proceeding to Whipple's or PPPD would seem to remain the best option.

For borderline resectable patients, or in resectable patients where surgery is unlikely to be performed because of lack of operating theatre or ITU space – consider neo-adjuvant hypo-fractionated (5-fraction) RT (refer to RT guideline document) or chemoradiotherapy (CRT) as bridge to surgery once ITU bed occupancy rates begin to decrease - the proposed alternative regimen to conventionally fractionated CRT is 36Gy/15# concurrent chemoradiotherapy (CRT) with daily capecitabine (Mon-Fri) (modified from PREOPANC) (7). These hypofractionated regimes would carry the theoretical advantage of reducing hospital visits, and concurrent capecitabine is minimally immunosuppressive. For RT guidance for the 15 fraction and 5 fraction regimens please visit www.uppergicancer.com/pancreatic-cancer

*Summary points:*
*a. Consider expediting planned surgical resection prior to predicted surge in ITU bed occupancy.*
*b. Consider hypofractionated neo-adjuvant SBRT (25-35Gy/5#) or CRT (36Gy/15# with capecitabine). Consider prospective data collection.*

#### 4.1.2. Adjuvant (see Fig on chemotherapy risk and COVID below)

Decisions relating to adjuvant therapy in this context likely to be nuanced. Use of adjuvant chemotherapy in older patients (>70 years) or those with comorbidities is likely to confer considerable risk, and should be avoided (Table 2). Adjuvant mFOLFIRINOX may be considered in fit younger patients where incremental benefit of post-operative chemotherapy can be justified despite increased risks posed by COVID. Factors that may favour intervention would include young age (<60 years) with no co-morbidity, particularly if there is poor prognostic features on histology. Decision regarding adjuvant therapy in patients aged 60-69 years should be considered carefully. If following discussion with patient, adjuvant treatment is favoured, consider delay of 12 weeks post surgery prior to commencing therapy (ie to tide over the peak of the pandemic). Use prophylactic GCSF with

chemotherapy. Patients must be carefully counselled regarding increased risks of death or severe complications if they were to contract COVID during treatment.

*Summary points: a. Consider not giving adjuvant chemotherapy to patients >70 years*
*b. Consider using mFOLFIRINOX only for younger patients (<60 years) with no co-morbidities with high-risk features*
*c. Adjuvant chemotherapy in 60-69 year age group should be made on individual patient basis*
*d. Consider using prophylactic GCSF in patients receiving mFOLFIRINOX*
*e. Consider delaying chemotherapy till 12 weeks post-operative (to avoid peak of pandemic)*

### 4.2. *LOCALLY ADVANCED PANCREATIC CANCER (LAPC)*

Typically patients with LAPC are treated with upfront chemotherapy with or without consolidation CRT. Overall median survival for patients receiving gemcitabine or GEMCAP induction chemotherapy is 12 months and in those who remain stable/responding after 4 months of chemotherapy, it is around 18 months(LAP07, SCALOP). Median OS of 24.2 months has been reported in a patient-level meta-analysis looking at FOLFIRINOX based chemotherapy with/without CRT (8). Upfront capecitabine based CRT (median OS 14.3 months) (9) or hypo-fractionated (5-fraction) radiotherapy (13.9 months)(10) may be less immunosuppressive options with reasonable outcomes, and may allow us to defer the onset of additional chemotherapy till after COVID-19 peak.

Decision regarding starting upfront chemotherapy (particularly FOLFIRINOX) vs upfront RT/CRT will have to be clinical decision in discussion with patient, considering age and co-morbidities, risks of the regimen itself and likelihood of contracting COVID (fig 1, table 2). Where CRT is being considered, a hypofractionated course (45Gy/15 fractions with capecitabine) would be preferred to minimize hospital visits. An alternative regimen of RT alone (SBRT, 25-35Gy/5 fractions) may also allow holding off immunosuppressive chemotherapy for a period of time in patients considered to be of particularly high risk of death or severe complications of COVID-19, or in exceptional circumstances, to ease excessive pressure on NHS resources. For RT guidance for the 15 fraction and 5 fraction regimens please visit www.uppergicancer.com/pancreatic-cancer/.:

*Summary points:* *a. Consider using mFOLFIRINOX only for younger patients (<60 years) with no co-morbidities.*
*b. Consider dose reduction and prophylactic GCSF in patients receiving FOLFIRINOX*
*c. Consider hypofractionated CRT(45Gy/15, capecitabine) or SBRT (25-35Gy/5 #) as holding regimen to delay onset of palliative chemotherapy in all other cases.*

### 4.3. METASTATIC DISEASE

#### 4.3.1. 1st line systemic therapy

| *Regimen* | *Median Survival* | *1-Year OS* | *Reference* |
|---|---|---|---|
| 5FU | 4.41 months | 2% | Burris, JCO, 1997 |
| Gemcitabine | 6.6 months | 22% | MPACT trial, von Hoff, NEJM, 2013 |
| Gemcitabine-nab-Paclitaxel | 8.7 months | 35% | MPACT trial, von Hoff, NEJM, 2013 |
| FOLFIRINOX | 11.1 months | 48.4% | Conroy et al, NEJM, 2011 |

Benefits of palliative chemotherapy is marginal for most patients, with a median improvement in survival of around 3-4 months (6 months for FOLFIRINOX). Factors that may change the balance of decision to treat include those relating to poor outcome with COVID-19 (e.g. older age, cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, performance status of 2). Risks may outweigh benefit in many patients and the decision to begin any chemotherapy should be made in the context of potential COVID-aggravated risk (fig 1, table 2).
If initiating systemic therapy, consider dose reduction, prophylactic gCSF and early imaging to assess response to systemic anti-cancer therapy. Patients on chemotherapy who have achieved partial response, consider break from chemotherapy (with imaging follow-up).

*Summary points:*
*a. Consider palliative chemotherapy in highly selected patients who are most likely to benefit*
*b. Consider dose reduction and using prophylactic GCSF*
*c. Consider early imaging to assess response to SACT to enable early treatment discontinuation if not achieving benefit.*
*d. If responding disease consider temporary break of chemotherapy.*

#### 4.3.2. 2nd line systemic therapy
2nd line should not be initiated.

*Summary points:* *a. Consider not using 2nd line chemotherapy*

#### 4.3.3. Palliative radiotherapy
Consider reducing fractionation and use single fraction approaches

*Summary points:* *a. Consider 8Gy/1# as palliative doses, or seek alternative non-radiotherapy based approaches to disease palliation.*

### 5. CONSIDERATIONS BY TREATMENT MODALITY

#### 5.1. Systemic anti-cancer therapy
The National Health Service (NHS) has provided a *Clinical guide for the management of cancer patients during the coronavirus pandemic*. In this, patients are categorised and prioritised for systemic anti-cancer therapy by anticipated outcome, as follows:

Priority level 1: curative therapy with a high (>50%) chance of success
Priority level 2: curative therapy with an intermediate (15-50%) chance of success
Priority level 3: non-curative therapy with a high (>50%) chance of >1 year of life extension

Priority level 4: curative therapy with a low (0-15%) chance of success / non-curative therapy with an intermediate (15-50%) chance of >1 year life extension
Priority level 5: non-curative therapy with a high (>50%) chance of palliation / temporary tumour control but <1 year life extension
Priority level 6: non-curative therapy with an intermediate (15-50%) chance of palliation / temporary tumour control and <1 year life extension

These factors should be taken into account when weighing up service constraints against the provision of systemic therapies.

When using systemic therapies, consider use of GCSF as primary prophylaxis in order to reduce likelihood of admission.

Consider chemotherapy dose-reduction to reduce admission rates, as guided by the GO2 phase III trial.
In a modelling exercise, Williams et al identified potential harms in patients undergoing chemotherapy during the COVID-19 outbreak (**Fig. 1**).

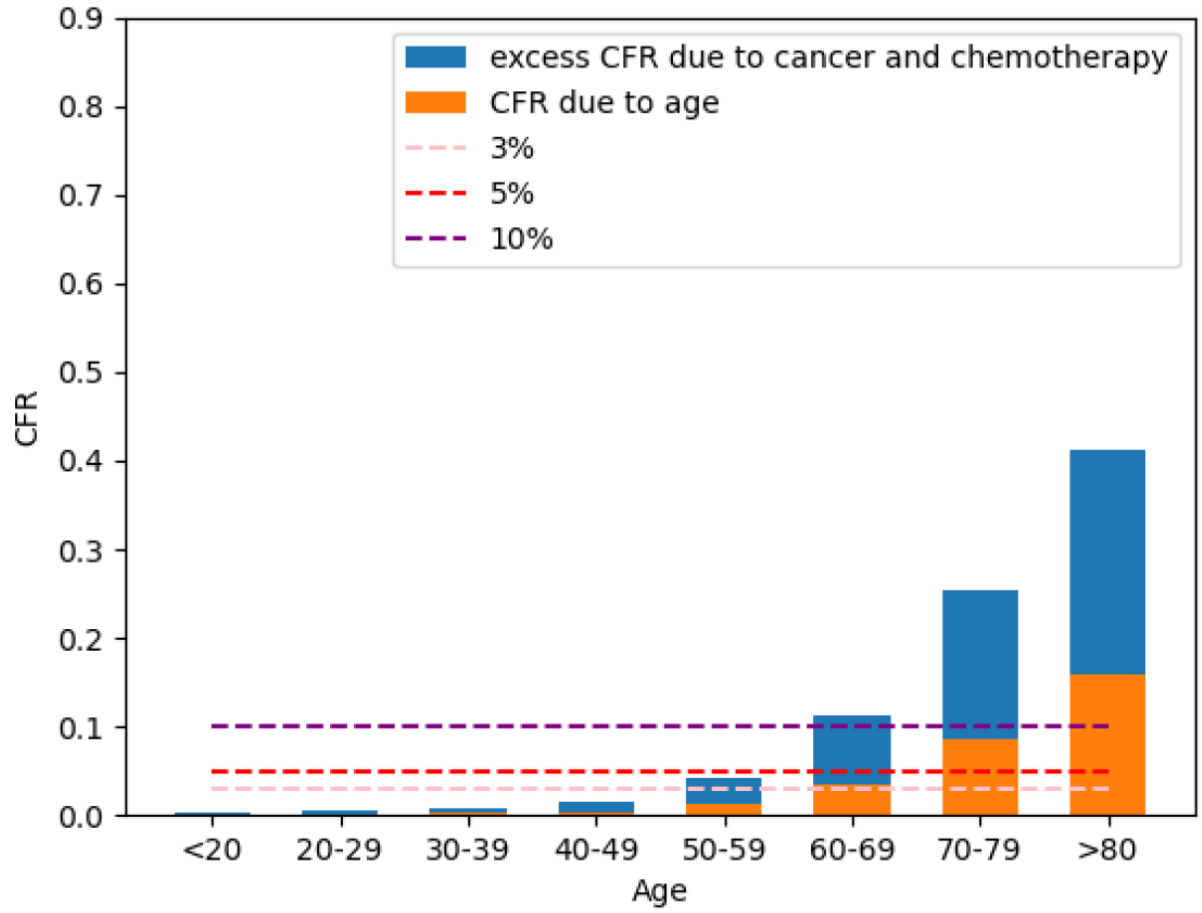


*Fig. 1: Optimistic model case fatality rates in patients with cancer infected with SARS-CoV-2, by age. Dashed lines represent common levels of benefit from chemotherapy in percent. (Williams et al, 2020).(11)*

| Age | Cases | Deaths | CFR(%) | CFR with Chemotherapy (%) |
|---|---|---|---|---|
| 0-9 | 480 | 0 | - | - |
| 10-19 | 672 | 1 | 0.086 | 0.23 |
| 20-29 | 4158 | 7 | 0.017 | 0.45 |
| 30-39 | 8453 | 19 | 0.22 | 0.6 |
| 40-49 | 10121 | 39 | 0.39 | 1.0 |
| 50-59 | 12547 | 144 | 1.15 | 2.9 |
| 60-69 | 11181 | 374 | 3.34 | 7.9 |
| 70-79 | 7001 | 592 | 8.46 | 16.9 |
| >80 | 3995 | 639 | 15.99 | 15 |
| Not reported | 565 | 18 | - | - |
| Total | 59173 | 1833 | 3.10 | 7.6 |

**Table 2.** Estimated case fatality rates by age group with chemotherapy

*Table 2. Estimated case fatality rates in patients on chemotherapy infected with SARS-CoV-2, by age (11)*

*Summary points: a. Refer to the NHS Clinical guide for the management of cancer patients during the coronavirus pandemic to inform decisions relating to chemotherapy use weighed up against service constraints.*
*b. Consider use of GCSF as primary prophylaxis in order to reduce admission likelihood.*
*c. Consider dose-reduced chemotherapy regimens to reduce admission likelihood.*
*d. Consider use of models, such as those by Williams et al, to inform decisions relating to chemotherapy provision during the COVID-19 outbreak.*

### 5.2. Radiotherapy

Robust local processes need to be in place to ensure that category 1 patients (which includes patients with pancreatic cancer receiving dCRT) can continue treatment uninterrupted even if they develop COVID-19 eg dedicated machine with optimal access, treat end of day with clean post treatment. Clinicians should nevertheless consider the risks of treatment interruption from COVID-19 infection and whether the potential resultant reduction in treatment efficacy changes the risk : benefit profile of delivering that treatment. Consider hypofractionated RT/CRT wherever possible.

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