1. **Study Background**

The incidence of oesophageal adenocarcinoma (OAC), or cancer of the gullet, is increasing faster than any other adult cancer. The disease affects approximately 2000 Australians per year and the majority of patients present with advanced cases that cannot be cured. Curative treatment for OAC involves major surgery that aims to completely remove the cancer. Due to the location of the oesophagus, the surgery involves removal of most of the oesophagus and some of the stomach, requiring incisions in the abdomen, chest and sometimes the neck. It typically takes approximately 6-9 months for health-related quality of life to return to normal after the surgery.

Unfortunately, despite improvements in surgical outcomes (death following surgery now occurs in <5%) remission following treatment is often short lived. OAC recurs for the majority, causing death in >80% of patients treated with curative intent. OAC relapses may occur in the site of the surgery (local relapse) or at other sites spread via the bloodstream, most commonly the liver (distant relapse). All relapses are incurable at the present time.

In an attempt to improve survival, pre-operative chemotherapy (CTX) or chemoradiotherapy (CRT) are the standards of care for operable OAC. The Australasian Gastro-intestinal Trials Group (AGITG) and NHMRC Clinical Trial Centre (CTC) recently performed an analysis of all trials comparing surgery alone with pre-operative CTX or CRT showing an absolute 2-year survival benefit of 7% for pre-operative CTX and 13% for CRT. Analyses relating to OAC only, reported pre-operative CTX provided a similar survival benefit to pre-operative CRT. However, pre-operative CRT can be associated with increased operative risk. Hence, there is debate regarding the most effective pre-operative therapy for patients with operable OAC with more data required to guide clinical decisions.

The largest study of pre-operative therapy for OAC (OEO2) was conducted in the United Kingdom (802 patients). That study randomly assigned patients to surgery alone or pre-operative chemotherapy with cisplatin and 5-fluorouracil (CF) administered over 6 weeks, followed by surgery. Long-term results have reported a significant improvement in 5-year survival: 23% for pre-operative CF, compared with 17% for surgery alone. More recently, another large UK trial provided an alternative peri-operative chemotherapy regimen using epirubicin (E) and CF for patients with gastric, and lower oesophageal adenocarcinoma.

The additional benefit of radiation therapy to pre-operative chemotherapy remains controversial. A recent German study (Stahl et al) compared CF-based chemotherapy (15 weeks) followed by surgery or CF-based CRT (15 weeks) followed by surgery OAC. In this study, preoperative CRT improved 3-year survival rate to 47% from 28% for preoperative CTX. It may be that the poor survival seen for CTX in this trial may have been due to the length of the pre-operative treatment (15 weeks). For patients not responding to the therapy, the additional 9 weeks of therapy compared with the OEO2 regimen (6 weeks) merely represents a delay in surgery whereas patients in the CRT arm were receiving some local therapy (RT) preoperatively.

In contrast, the Princess Alexandra Hospital, Brisbane, has recently completed a randomised phase II trial of pre-operative CF chemotherapy (6 weeks) with or without radiation therapy (n=76). There was no significant difference in overall or progression-free survival. Hence, there is a pressing need to define the role of modern radiation therapy in the treatment of operable oesophageal cancer in the context of adequately performed surgery. The role of chemotherapy based on Cisplatin is accepted. Data from OEO2 and the PAH phase II trial suggest CF is the logical first choice pre-operative treatment for resectable OAC based on both survival and tolerability.
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**Oesophageal Cancer and Histological Response**
Evidence of CT, RT, or CRT having an effect on cancer is referred to as a response to treatment. This is typically assessed by the pathologist who examines the surgically removed tumours for evidence of cancer cell death. This is referred to as a histological response and it is a significant indicator of survival in oesophageal cancer. Obtaining a histological response to pre-operative therapy is therefore desirable for patients and there is a clear need to increase the proportion of patients responding to pre-operative therapy.

**Oesophageal Cancer and Early FDG-PET Response**
Histological response is an end-point that is obtained after the completion of the selected pre-operative therapy and the operation. Thus patients in whom pre-operative therapy has not had an effect are only identified when the options to change therapy are limited and can only be given post-operatively. Given only 50-60% of patients are fit for post-operative chemotherapy, this option has limited value.
FDG-PET scanning uses radioactively-labeled glucose to detect cancers and is routinely used in the initial assessment of patients with OAC. Essentially, FDG-PET scan detects the level of metabolic activity in cancers. Recently, an early metabolic response to pre-operative therapy (determined by a reduction in the primary cancer activity on FDG-PET scan performed 14 days after the start of CTX compared with the activity seen on FDG-PET scan performed before CTX) has been shown to predict histological response and survival. The challenge remains to improve the proportion of responders to pre-operative therapy while limiting toxicity and avoid delay to curative surgery. These data suggest that FDG-PET scanning on day 14 after the commencement of CTX can identify patients that are not responding to the first choice pre-operative therapy, thus allowing a timely consideration for a change in that therapy.

Subsequently, Lordick et al reported the only clinical study that has modified therapy based on an early metabolic response. In that study, patients that showed an early metabolic response to the first cycle of pre-operative CTX then received further CTX then resection with 2-year survival of 75%. Patients that did not show an early metabolic response on the day 14 PET scan received no further CTX and went directly to surgery with 2-year survival 60% and no histological responses. In summary, early metabolic non-responders to CF-based chemotherapy are a well-defined OAC patient group with poorer response rates and poorer survival. It is logical to try to improve the survival of the poor prognosis, non-responder group. No one has done this study and it is the basis of this trial.

**Improving Response Rates: Future Directions**
Recent data from clinical trials have revealed that docetaxel (D) in combination with cisplatin and/or 5-FU/capecitabine (DCF or DCX) has activity in advanced oesophageal and gastric cancer. In Australia, AGITG have demonstrated the benefit of weekly docetaxel based therapy in combination with infusion fluorouracil in advanced gastric cancer with acceptable toxicity. However, regimens containing D are generally reported to have higher toxicity than CF alone. Docetaxel in combination with C and F has been administered with and without radiation in phase II clinical trials. Both approaches have been tolerable with encouraging response rates. These newer regimens do not appear to have increased the risks of surgery.

The question being addressed by this trial is whether changing the pre-operative therapy regimen improves the response rates for patients that fail to demonstrate an early metabolic response after the first cycle of treatment.
2. **Rationale for the study**

The outcomes for early metabolic non-responders have been well defined and are known to be poor. The ability to identify patients not responding to the selected chemotherapy represents a significant advance in the management of patients with operable/removable OAC. There is a genuine clinical need to increase the proportion of patients responding to chemotherapy and improve the outcome of those that fail to respond to the initially selected therapy. In contrast to the approach taken by Lordick et al, we believe it is now time to begin a prospective clinical trial aimed at improving outcomes for patients that fail to show an early metabolic response to pre-operative CF chemotherapy. We have developed a randomised, non-comparative phase II trial to determine whether the addition of docetaxel +/- radiotherapy can significantly improve the histological response rate for early metabolic non-responders compared with historical outcomes if the same chemotherapy had been continued. This study is not intended to compare the efficacy of the experimental regimens, but rather to determine whether both approaches, one or none could be used for non-responders, with acceptable toxicity and health-related quality of life (HRQoL) outcomes. This novel trial design represents a change in the pre-operative therapy paradigm. The molecular substudy aims to identify biomarkers of response. The investigators seek to identify non-responders to CF at the time of initial biopsy so that a more active regimen, identified by the present study, may be selected initially.

3. **Please indicate if there are any restrictions to the study.**

   **Exclusion Criteria**
   1. Metastatic disease
   2. Tumour located in the cervical oesophagus.
   3. Tumour is predominantly within the stomach.
   4. Evidence of tracheo- or broncho oesophageal fistula.
   5. Inadequate haematological function
   6. Inadequate liver or renal function
   7. Previous radiation therapy to the chest, no previous chemotherapy for at least 5 years.
   8. No previous malignancy for the previous 5 years apart from non metastatic SCC of the skin, BCC or carcinoma in situ of the cervix.
   9. Pregnant or lactating.

4. **Proposed study design (please include sample size, # of sites, proposed recruitment and follow-up duration)**

   Eligible patients with operable OAC will receive one cycle of cisplatin (C) and 5-fluorouracil (F) initially (day 1). Early metabolic response will be assessed on day 14. Patients whose tumours show an early metabolic response (>35% reduction in SUVmax on day 14 FDG-PET scan compared with pre-treatment scan) will receive one more cycle of C and F, followed by surgery. Metabolic non-responders will be randomised to:

   **Arm A:** 2 cycles of CF with the addition of weekly docetaxel (D) followed by surgery (DCF).
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Arm B: 2 cycles of CF with the addition of weekly docetaxel (D) and concurrent external beam radiotherapy (total dose 45Gy) followed by surgery (DCF + RT).

Sample Size: The total number of patients needed for the entire study is 150, with the aim of randomizing 82 patients to the two treatment arms (41 patients in each arm).

Number of sites: The study is underway at the Princess Alexandra Hospital, Brisbane. It is intended to open the trial at additional sites in Brisbane, Sydney, Melbourne, Adelaide and Perth.

5. Quality of life issues

To date, retrospective studies have shown that pre-operative therapy has a detrimental impact on patients’ self-reported HRQoL scores. However, the impact lasts only for the duration of the therapy and returns to baseline before surgery. Short-term studies reporting HRQoL scores up to one year after pre-operative therapy and surgery have not found a significant impact on self-reported HRQoL compared with surgery alone. Similarly, no differences were identified between patients receiving CRT or CTX preoperatively. In the advanced setting, Ajani and others reported that patients receiving DCF maintained higher HRQoL scores compared with patients receiving CF in a randomised phase III trial.

The proposed trial includes a HRQoL substudy. For diseases such as oesophageal cancer where the outcomes are poor and the differences between treatment modalities are modest, HRQoL data are important and may guide physician and patient choice. Knowledge of the HRQoL impact of treatment, particularly in a poor prognostic group such as early PET-non-responders to pre-operative therapy, will provide much needed data for future study design as well as practical treatment decisions in the clinic.

6. Additional comments