**PAPILLON TREATMENT ON-GOING RESEARCH** Professor A. Sun Myint

Although Papillon treatment for rectal cancer has been around for over 80 years (since late 1930s), this treatment technique is still not regarded as the standard of care in the UK except for patients with early rectal cancer not suitable for surgery (IPG 532, NICE)[1]. The first randomised trial (Lyon96-02) was carried out by Prof Jean Pierre Gerard while he was working in Lyon. The results were published in the Journal of Clinical Oncology following an oral presentation at the prestigious 45th Annual Meeting of the American Society of Therapeutic Radiology and Oncology (ASTRO) at Salt Lake City, UT, on 21st October, 2003 (Gerard et al. 2004)[2]. This trial evaluated patients with rectal carcinoma located in the lower rectum, staged T2 or T3, Nx, or M0.

The patients were randomly assigned to one of two groups: preoperative external-beam radiotherapy (EBRT; 39 Gy in 13 fractions over 17 days) versus the same EBRT with boost (85 Gy in three fractions) using endocavitary contact x-ray (Papillon). Patients in both arms of the trial had surgery. The main end point was improvement in sphincter preservation with avoidance of a permanent stoma. Between 1996 and 2001, 88 patients were enrolled onto the study. A significant improvement was seen in favour of the contact x-ray (Papillon) boost for complete clinical response (24% v 2%) and for a complete or near-complete sterilization of the operative specimen (57% v 34%). A significant increase in sphincter preservation was also observed in the boost group (76% v 44%; P 0.004). At a median follow-up of 35 months, there was no difference in morbidity, local relapse and 2-year overall survival. The trial concluded that dose escalation with endocavitary irradiation (Papillon) increased tumour response and sphincter preservation with no detrimental effect on treatment toxicity and early clinical outcome. However, there were several weakness in this trial. The number of patients in each arm was relatively small with only 43 patients in the EBRT only arm and 45 patients in the combined EBRT + Papillon boost arm. In addition, the EBRT regime used was not an internationally accepted standard dose and fractionation (39Gy/13 fraction/17 days). The standard dose and fractionation currently used is 50Gy in 25 fractions over 25 days. Chemotherapy which has become the standard of care for neoadjuvant (preoperative) radiotherapy was not included in both arms of the trial. The results did not change clinical practice.

Since 2005, international radiation experts have met regularly to discuss future trials on Papillon. In 2008, the International Contact Radiotherapy Network (ICONE) was formed at one of the Papillon meetings held in Nice. Prof J P Gerard was elected as its first president. In 2013, following World Rectal Cancer Congress in Rome, Prof Arthur Sun Myint was elected as its president. Then in 2018, Dr Amandeep Dhadda took over the role of the president of ICONE. A new randomised trial to establish Papillon as a standard of care in selective patients was discussed among the members in many of these ICONE meetings. Finally, in 2013 a European phase 3 randomised trial OPERA (Organ Preservation for Early Rectal Adenocarcinoma) was agreed[3]. Funding of Euro 0.5 m from the French government research authority was awarded in 2014 and OPERA trial randomisation started in June 2015.

**OPERA (Organ Preservation for Early Rectal Adenocarcinoma) NCT02505750**

**Brief Summary:**

The investigators propose to conduct a randomised study on cT2, cT3a-b tumours less than 5cm using two different techniques of radiotherapy boost following neoadjuvant chemoradiotherapy (EBCRT) (CAP45): EBRT (9 Gy/5 fractions) or CXB (90 Gy/3 fractions). The endpoint will be organ preservation at 3 years without non-salvageable local pelvic recurrence. The proof of this concept will be of most benefit for all patients but especially for older patients who usually are not fit for or keen to undergo major surgery.

The hypothesis of this study is to determine if the addition of an endocavitary boost with CXB after standard treatment with EBCRT, increases the chance of rectum and anus preservation by 20%- (organ preservation in control arm 20%, in experimental arm 40%).

**Active Comparator Arm A** : EBRT 45 Gy/capecitabine + EBRT boost

3D conformal EBRT 45 Gy (1.8Gy/fraction/5 weeks) with concurrent chemotherapy using capecitabine (825 mg/m2 bid, on radiation days i.e. Mon-Fridays).

A cone down EBRT targeting the GTV will deliver a boost dose of 9 Gy in 5 fractions. On week 14 after the start of treatment, the tumour response evaluation will guide the final strategy: surgery (radical TME or local excision) or watch-and-wait (W-W). Final decision on treatment will be made at week 24 (6 months from randomisation).

Radiation: 3D conformal EBRT

External Beam Radiation Therapy

Drug: Capecitabine

**Experimental Arm B**: EBRT 45 Gy/capecitabine + CXB boost

Arm B divided in 2 sub-groups depending on the tumour diameter:

B1: If the tumour is < 3cm, a CXB boost dose (90Gy/3 fractions/4 weeks) will be initially delivered to the tumour. After 2 weeks rest, patients will receive 3D conformal EBRT 45 Gy (1.8 Gy/fraction/5 weeks) with concurrent chemotherapy using capecitabine (825 mg/m2 bid, on radiation days). Clinical evaluation will be performed 3 weeks after the end of irradiation (week 14) and will guide the final strategy (surgery or W-W) as in arm A.

B2: If the tumour is ≥ 3 cm, patients will receive EBRT first 45 Gy (1.8 Gy/fraction/5 weeks) with concurrent chemotherapy using capecitabine (825 mg/m2 bid, on radiation days).

A CXB boost dose (90 Gy/3 fractions/4 weeks) will be delivered to the residual tumour, after a rest of 2 weeks. On week 14 after the start of treatment, the tumour response evaluation will guide the final strategy (surgery or W-W) as in arm A. Adjuvant chemotherapy will be left to institution choice.

The main objective is to demonstrate that neoadjuvant chemoradiotherapy in combination with a boost given with CXB (Arm B) is superior to the same neoadjuvant therapy plus a boost with EBRT alone (Arm A) in terms of rectum (organ) preservation without non salvageable local disease at 3 years post treatment start, or permanent deviating stoma.

**Study Design**: Open-label, phase III, prospective, multi-centre, international, randomised 1:1, 2 arm study designed to evaluate the efficacy of a CXB boost versus an EBRT boost.

**Outcome Measures**

Primary Outcome Measures:

1. Rate of rectum preservation either with local excision or watch and wait strategy after neoadjuvant treatment without non salvageable locally progressive disease at 3 years post treatment, or permanent stoma. [Time Frame: 3 years post treatment]

The primary analysis will take place when approximately 138 events have occurred.

2. The evaluation of the rate of rectum preservation without progressive local disease at 3 years will be performed using a Log rank test stratified by center.

Secondary Outcome Measures:

1. Clinical Complete Response (assessed by digital rectal examination, endoscopy with photos and MRI) [Time Frame: Week 14]

2. Overall Survival [Time Frame: 3 years post treatment]

3. Time between date of randomisation and date of death due to any causes. Patients who were not reported as having died at the time of the study will be censored at the date they were last known to be alive

4. Disease-free survival [Time Frame: 3 years post treatment]

5. Time between date of randomisation to time of recurrence, either local or distant metastasis or death due to any cause). Patients without an event will be censored at last date the patient was known to be disease-free. Recurrence of rectal cancer will be based on tumour assessment made by investigator

6. Tumour regression score on the operative specimen [Time Frame: week 24]

**Other Outcome Measures:**

1. Rate of sphincter conservation [Time Frame: 3 years post treatment]

2. Treatment toxicity [Time Frame: 3 years post treatment]

3. Early and late toxicity by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

4. Bowel function [Time Frame: 3 years post treatment]

5. Bowel function by modified Low Anterior Resection Score (LARS)

6. Quality of Life [Time Frame: 3 years post treatment]

7. Quality of life questionnaire (QLQ): QLQ-C30 and colorectal (CR) QLQ-CR29 questionnaires

**Eligibility Criteria**

**Inclusion Criteria:**

1. Adenocarcinoma of the rectum classified clinically T2, T3a, T3b (penetration in the mesorectal fat between 1 to 5 mm) by TNM classification (Tumour Node Metastases), < 5 cm largest diameter, < half rectal circumference (by MRI staging), N0-N1 (any node < 8 mm diameter on MRI), M0 Operable patient

2. Tumour accessible to endocavitary contact X-Ray Brachytherapy with a distance from the lower tumour border to the anal verge ≤ 10cm

3. Age 18 years or above

4. No comorbidity preventing treatment

5. Adequate birth control

6. Patient having read the information note and having signed the informed consent

7. Follow-up possible

**Exclusion Criteria:**

1. Inoperable patient

2. T1, T3cd, T4, T≥ 5cm, T≥ ½ circumference

3. Patient N2 at diagnosis or N1 with any node > 8 mm diameter

4. Patient presenting metastasis at diagnosis

5. Previous pelvic irradiation

6. Tumour with extramural vascular invasion

7. Simultaneous progressive cancer

8. Tumour invading external anal sphincter and within 1 mm, and the levator muscle

9. Patient unable to receive CXB or CRT

10. Tumour with poor differentiation (G3)

11. People particularly vulnerable as defined in Articles L.1121-5 to -8 of the French Healthcare Code, including: person deprived of freedom by an administrative or judicial decision, adult being the object of a legal protection measure or outside state to express their consent, pregnant or breastfeeding women

12. Any significant concurrent medical illness that in the opinion of the investigator would preclude protocol therapy

13. Patient with history of poor compliance or current or past psychiatric conditions or severe acute or chronic medical conditions that would interfere with the ability to comply with the study protocol

14. Concurrent enrolment in another clinical trial using an investigational anticancer treatment within 28 days prior to the first dose of study treatment

**Trial progress update**

Up to 21st June 2020 we have randomised 146 patients with 144 evaluable patients from 10 centres in Europe (5 centres from the UK). An independent data monitoring committee met initially on 14thApril 2019 and again on 24th June 2020 to review the data, initially on the first 80 patients and later on all 146 randomised patients. IDMC recommended to close the trial as the number of patients randomised so far has sufficient power to show significant differences between two arms of the trial. We will continue to monitor the patients closely for the next 3 years as per trial protocol. We hope to report first on the safety of surgical salvage and the toxicity after a minimum follow up of one year. The main trial results will be reported in 2023.

**References**

1**.** Low energy contact X ray brachytherapy (the Papillon technique) for early stage rectal cancer NICE 2015 (IPG 532) http://nice.org.uk/guidance/ipg532

2. Jean-Pierre Gerard, Olivier Chapet, Chantal Nemoz et al. Improved Sphincter Preservation in Low Rectal Cancer With High-Dose Preoperative Radiotherapy: The Lyon R96-02 Randomized Trial. J Clin Oncol, 2004; 22:2404-2409. http://doi:10.1200/JCO.2004.08.170.

3. European phase III study comparing a radiation dose escalation using 2 different approaches: External beam radiation therapy versus endocavitary radiation therapy with contact x-ray brachytherapy 50 kilovolts (kV) for patients with rectal adenocarcinoma. **ID: NCT02505750.** https://www.clinicaltrials.gov/ct2/show/NCT02505750?term=contact+x-ray+brachytherapy&cond=Rectal+Cancer&cntry=FR&draw=2&rank=1