



# Organ Preservation for Early Rectal Adenocarcinoma: The OPERA European Trial to Bring Robust Evidence

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## Editorial

Surgery: cornerstone of rectal cancer treatment ... BUT!

The curative treatment of rectal cancer is based on radical TME surgery. It is well admitted that abdomino-pelvic-resection (APR) is a severe body mutilation due to permanent stoma. More and more it is recognized that even low anterior resection (LAR) is not providing a very good quality of life because the LAR syndrome is often present and distressful [1]. For that reason a new way of clinical research is aiming at curing rectal cancer with organ preservation and many expert colorectal surgeons are asking the question: "When not to perform radical TME surgery?" [2].

### Habr Gama and the "Watch & Wait" data base

Habr Gama was the first surgeon to question the use of TME surgery when after neoadjuvant treatment, radiotherapy and more recently chemoradiotherapy (nCRT), a pathological complete response was seen on the operative specimen. She developed an original strategy called "Watch & Wait". After nCRT a careful surveillance is performed mainly with digital rectal examination (DRE), rectoscopy and imaging (MRI, endorectal ultrasonography-ERUS). In case of CLINICAL complete response (cCR) a simple surveillance is proposed without any surgery (or with local excision for some institutions). This strategy is becoming adopted by many colorectal departments in the world. Majority of data of this strategy are collected in the IWWD (International watch and wait data base). Out of 756 patients registered [3] and with the Habr Gama data [4] the results achieved when treating T2-3 M0 patients are: a cCR is observed in nearly 40% of patients and at 3 years the local recurrence rate is close to 30%. Most of local recurrences are in the rectal wall and less than 5% in the peri-rectal lymph nodes. Such recurrences can usually be salvaged using TME surgery. It is not proven that these recurrences do not compromise survival. Contact X-ray brachytherapy (CXB): Safe and efficient to achieve cCR. This technique using a trans-anal endoscopic brachytherapy with superficial 50 kV X-rays was pioneered in the 1970s by Papillon who achieved a 90% local control with CXB when treating T1N0 tumors [5]. Further experiences gained in Lyon showed that similar high control rate with good bowel function could be achieved when combining for T2 -T3 N0 ≤4 cm diameter CXB and External beam radiotherapy (EBRT) [6]. The Lyon R96-02 randomized trial is the only trial which has demonstrated that when adding CXB to EBRT it was possible to achieve more cCR in T2-3 (29% vs. 2%) which translates at 10 years into more sphincter and organ preservation with no severe toxicity [7,8].

### Renaissance of CXB

In the late 1990s no more CXB machine was manufactured. It was only in 2010 that a British company designed new 50kV systems called Papillon 50<sup>TM</sup>. At the present time 11 Papillon 50 are used in Europe in 5 different countries to treat rectal cancer and this treatment is officially recognized as efficient for rectal cancer by national authorities (HAS in France and NICE in UK). Main results for organ preservation in T2T3 tumors treated with nCRT (45Gy to 50 Gy with concurrent capecitabine) and a CXB boost (90 Gy in 3 fractions) come from France [9] and UK [10,11]. Out of more than 300 treated patients during 2003-2016, a cCR was achieved in nearly 85% of patients and a local recurrence was seen in less than 15% with a good bowel function and no severe toxicity.

### OPERA trial to bring the evidence

The improved results in terms of organ preservation achieved with CXB are explained by two reasons. First it is now well documented that rectal adenocarcinoma is a quite radio-resistant tumor. In order to sterilized (only) 50% of T3 tumors a mean dose of 92 Gy is necessary [12]. Only using CXB such a high dose can be delivered to the tumor without exceeding rectal tolerance. Second,

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when the tumor's volume is large (diameter  $\geq$  5cm) the chances of cCR are <10% [13]. To hope for a good chance of organ preservation it is necessary to select strictly T2 or early T3a-b with no perirectal fat infiltration more than 5 mm in depth. Such tumors can be selected using MRI or ERUS. For decision making it is recommended to follow the ESMO guidelines and the sub-classification of T3 tumors into "good, bad and ugly" [14,15]. The OPERA randomized trial (ID-RCB:2014:A01851-46) is testing the hypothesis that adding a CXB boost to nCRT will improve organ preservation at 3 years (main end-point of the trial) from 20% to 40% (HR: 0.56). Inclusion criteria are: operable patient, T2 T3a-b N0 M0 distal-middle rectum. Tumor less than 5 cm in largest diameter. All the patients will receive nCRT (45 Gy+ capecitabine) and randomization will be between a boost with EBRT (9 Gy/1 week) or CXB (90 Gy/3 fractions). On week 14 after start of treatment all the patients will undergo a careful assessment of tumor response (DRE, Rectoscopy, MRI, etc.). In case of cCR a W&W (or local excision) will be proposed and a TME surgery will be performed in case of partial response. The trial is promoted by Centre Antoine Lacassagne in Nice and first patient was included in July 2015. At present time 35 patients have been included in France, UK, Sweden, Switzerland will accrue patients before June 2017. A total of 236 patients will be included before end of 2019[16].

## Conclusion

Organ preservation is becoming one of the main fields of research for rectal cancer treatment. The key point is to achieve cCR after neoadjuvant treatment. Evaluation and definition of cCR are crucial to make an optimal decision. Watch means to perform rectoscopy at regular (and close) intervals. This clinical exam is becoming a must for the radiation oncologists to perform CXB and is probably the more reliable (with the "bioprobe" i.e., DRE) to assess cCR.

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