Associazione Italiana Radioterapia Oncologica

A phase II trial with FOLFOXIRI and bevacizumab followed by chemoradiotherapy and bevacizumab in locally advanced rectal cancer (TRUST trial): A multicentric study

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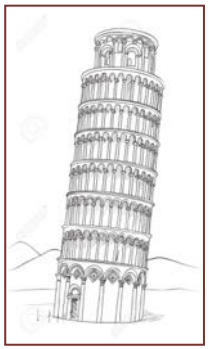

STUDY RATIONALE

- In pts with LARC preoperative CTRT is the standard treatment and is effective in local control
- The rate of distant relapses at 5 years is between 30% and 40% also in pts treated with adjuvant CT
- To improve the distant control of disease we propose a regime of neoadjuvant intensified CT followed by CTRT

STUDY DESIGN

FOLFOXIRI + bevacizumab (6 cycles, every 2 wks)

3 wks

Pelvic RT + CT (capecitabine) + bevacizumab

7-9 wks

Surgery (TME)

ENDPOINTS

PRIMARY ENDPOINT

2 years disease free survival

SECONDARY ENDPOINTS

- Rate of complete patological responses
- Rate of clinical responses
- Overall survival
- Safety

INCLUSION CRITERIA

- Histological diagnosis of rectal adenocarcinoma
- Age $\leq$ 70 with PS= 0-1 or Age 71-75 with PS=0
- Resectable advanced rectal cancer with:
  cT3-T4; anyT,cN+
- No metastasis

PATIENTS CHARACTERISTICS

March 2012 - April 2015 → 48 pts enrolled by:

- ✓ Pisa-Pontedera (35 pts)
- ✓ Padova (10 pts)
- ✓ Siena (3 pts)

Median age: 53 (range 30-74)

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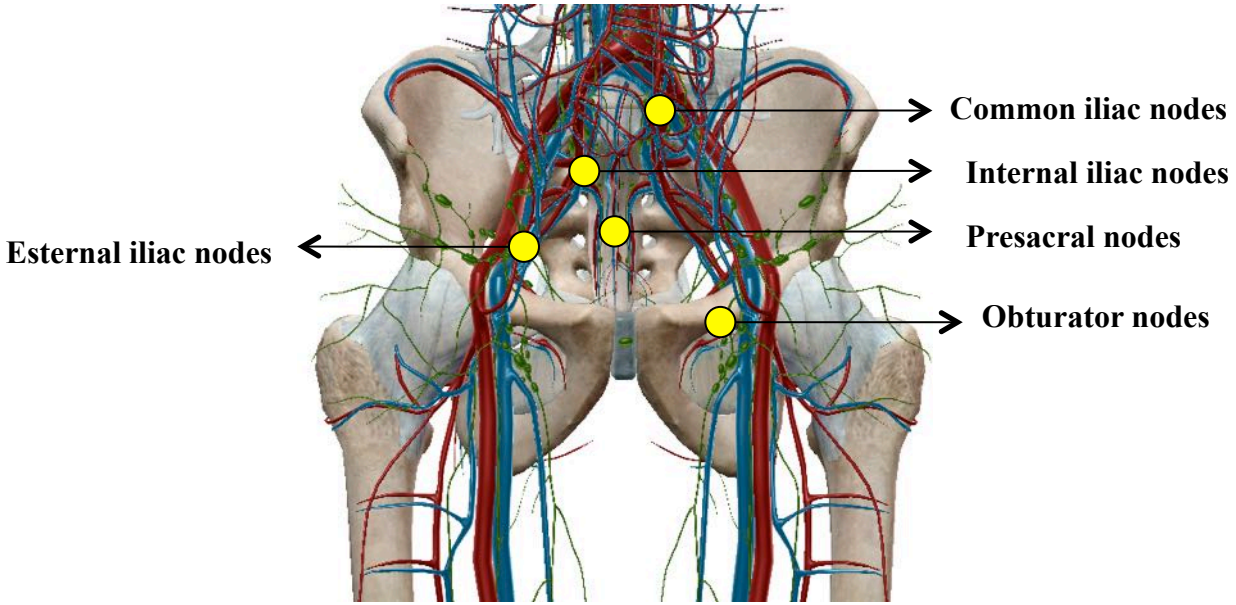
CLINICAL STAGE	% of PTS
cT2N+	4,2
cT3N0	12,5
cT3N+	47,9
cT4N0	4,2
cT4N+	31,2

SITE OF T	% of PTS
LOW	56,2
MEDIUM	39,6
HIGHT	4,2

* *All pts were staged with MR, EUS and Total Body CT-scan*

CONCOMITANT TREATMENT

RT Volume:



- **RT Dose**: 5040 cGy / 28 ff
- **RT Tecnique**: 3DCRT or VMAT (depending on anatomy)
- Capecitabine: 825 mg/sqm BID (mon-sun)
- Bevacizumab: 5 mg/kg every two weeks

CT-INDUCTION: TOXICITY

- 46/48 pts have compleated the CT-induction phase
- 1 patient died after the first cycle of CT from bowel perforation
- 1 patient decided to interrupt CT because of acute renal failure

TOXICITY	G1	G2	G3	G4
vomit	17	8,3	0	0
diarrhea	35	19	8,3	4,2
stomatitis	35	17	4,2	0
neurotoxicity	52	15	0	0
H-F syndrome	8,3	10	0	0
neutropenia	10	27	23	19
thrombocytopenia	19	0	2,1	0
anemia	67	6,3	0	0

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First 15 pts

TOXICITY	G1	G2	G3	G4
diarrhea	31	15	15	0
proctitis	15	62	23	0
rectal bleading	23	54	0	0
H-F syndrome	0	46	23	0
radiodermatitis	54	38	7,7	0
anemia	69	0	0	0
thrombocytopenia	38	0	0	0
leukopenia	46	0	0	0

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rectal bleading	23	54	0	0
H-F syndrome	0	46	23	0
radiodermatitis	54	38	7,7	0
anemia	69	0	0	0
thrombocytopenia	38	0	0	0
leukopenia	46	0	0	0

After capecitabine dose reduction to 75%

TOXICITY	G1	G2	G3	G4
diarrhea	57	6,7	0	0
proctitis	60	6,7	6,7	0
rectal bleading	37	0	0	0
H-F syndrome	20	6,7	0	0
radiodermatitis	50	17	0	0
anemia	43	0	0	0
thrombocytopenia	23	0	0	0
leukopenia	37	17	0	0

PERIOPERATIVE TOXICITY

- 42/45 pts underwent surgery (39 evaluable)
- 2 pts are waiting for surgery
- 1 patient had PD and died before surgery

TOXICITY	% of PTS
Dehiscence	12,8
Fistula	5,1
Sub-occlusion	2,6
Hematoma of abdominal muscles	2,6
Peritonitis and Sepsis	2,6

PERIOPERATIVE COMPLICATIONS: 25,7 % OF PTS !!

RESULTS

	Clinical responses after CT-induction	Clinical responses after CT-RT
CR	-	15%
PR	77%	73%
SD	19%	10%
PD	-	2%

- **After Surgery** (39 pts evaluable) **: pCR:33%**

- **After a median F-U of 17 months:** - 18% of pts had distant mts

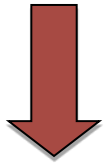
  - 2,6% of pts had locoregional failure

CONCLUSIONS

- Intensified CT-induction (plus bevacizumab) followed by RTCT seems to increase the rate of pCR

- Can we expect an increase also in DFS?

Preliminary data



2 yy DFS estimated with Kaplan Meier test: 72%

CONCLUSIONS

…And...What about the safety?

- After 6 cycles of CT-induction the toxicity during concomitant phase was remarkable *(probably because of folates cumulative-dose)* and required a particular patient care

- The rate of perioperative toxicity was higher than our historic group (*probably due to the use of bevacizumab*)

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…And...What about the safety?

- After 6 cycles of CT-induction the toxicity during concomitant phase was remarkable *(probably because of folates cumulative-dose)* and required a particular patient care

- The rate of perioperative toxicity was higher than our historic group (*probably due to the use of bevacizumab*)

… *so* …

Our opinion is that the use of intensified regimen of neoadjuvant CT should not be used yet in clinical practice.
Longer follow-up time and new clinical trials are required.

Grazie per l'attenzione...