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August 2011

J-POUCH vs STRAIGHT
Randomised Multicentre Clinical Trial

Colonic J-pouch reconstruction versus straight colorectal anastomosis after low anterior resection for rectal cancer: impact on anastomotic leak, bowel function and quality of life

NCI's PDQ Cancer Clinical Trials Registry
USP-1935P

Introduction

The J-POUCH VS STRAIGHT trial was launched over a year and a half ago and until now 150 patients have been enrolled. The study is supported by renowned scientific societies such as the SICCR and the SICO, and aims to assess whether the incidence of major anastomotic leak, following low-anterior resection for rectal cancer, is reduced by using the J-pouch reconstruction technique as opposed to straight colorectal anastomosis.

Currently, in Europe and in the United States, there are four multicenter clinical trials, as well as ours, with the primary aim of evaluating the role of the type of anastomosis in restoring the bowel function and capacity of the neorectum after a low anterior resection for rectal cancer.

The SAVE trial (Charite University, Berlin, Germany), started in June 2010, estimates to enrol 306 patients with histological proven middle to low rectal cancer requiring TME, with or without neo-adjuvant radio-chemotherapy. Patients are randomized to receive side-to-end anastomosis, considered the experimental intervention, or J-pouch as control intervention.

The Cleveland Clinic randomized trial (Ohio) too compares the functional outcome and quality of life in low rectal cancer patients after a side-to-end anastomosis, experimental procedure, or after a J-pouch anastomosis, standard group. The accrual of an estimated 400 patients started in March 2009.

The Swiss Group for Clinical Cancer Research is running a trial with the primary objective to evaluate side-to-end anastomosis vs J-pouch anastomosis vs straight anastomosis as rectal reconstruction techniques after TME in terms of defecation quality and frequency in patients with rectal cancer. This randomized trial compares 3 different methods of rectal reconstruction since the most effective method after surgery is still not known. A total of 282 patients should be recruited from 2005 to 2012.

Finally, a Dutch study (Academisch Medisch Centrum, Universiteit van Amsterdam) is randomizing 100 patients to receive a J-pouch coloanal anastomosis as experimental technique or side-to-end anastomosis, as control procedure to assess whether the J-pouch anastomosis is better in improving functional results after rectal surgery.

Our study is, until now and to the best of our knowledge, the only one that aims to associate the type of reconstruction with anastomotic leak, which represents the most serious surgical complication in terms of consequences for the patient having a potential clinical impact in the long term period. The number of participating centers demonstrates the interest in this clinical question.

Contents

Progress of the study

Patient recruitment proceeds as planned and data collection has improved too. About 84% of case report forms with baseline and surgical data have been completed and sent to the coordinating centre. The main limitation is represented by the completeness and timeliness of the anastomosis evaluation, particularly at 30 days from surgery. Please remember that it is necessary to fill in the anastomosis form within 1 month from surgery and subsequently at 6 and 12 months. Moreover, the anastomotic complications have to be investigated according to radiologic and endoscopic examination. Rectal exploration is not permitted.

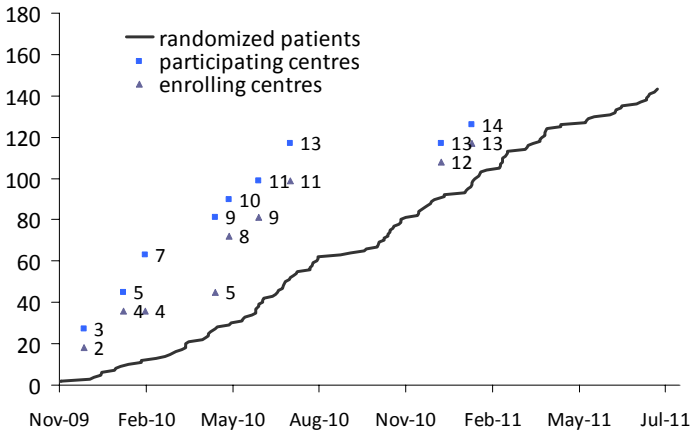
We would also like to remind everyone to take specific care in the accuracy and timing of data collection since complete and consistent data are the basis of a successful and good research.

Reports

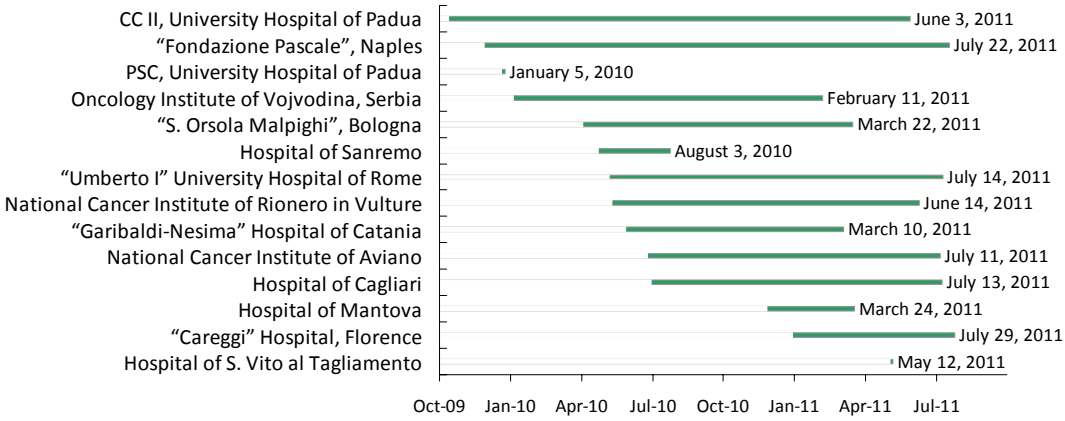
Accrual

As of 30th July 2011, 144 patients have been randomized. Fifteen clinical centres are involved in the study and 8 centres are awaiting local Ethic Committee approval.
The table below shows the distribution of randomized patients stratified according to clinical centre.

Participating centres	Date 1st enrolment	N° patients
Clinica Chirurgica II, University Hospital of Padua	26/10/09	12
"Fondazione Pascale" National Cancer Institute of Naples	10/12/09	49
Patologia Speciale Chirurgica, University Hospital of Padua	05/01/10	1
Oncology Institute of Vojvodina, Serbia	16/02/10	14
"S. Orsola Malpighi" University Hospital of Bologna	14/04/10	5
Colonproctologia, Hospital of Sanremo	03/05/10	4
Chirurgia d'urgenza retto, "Umberto I" University Hospital of Rome	17/05/10	4
National Cancer Institute of Rionero in Vulture	20/05/10	12
Chirurgia Oncologica, "Garibaldi-Nesima" Hospital of Catania	07/06/10	10
Chirurgia Generale Oncologica, National Cancer Institute of Aviano	05/07/10	6
Chirurgia Generale, Hospital of Cagliari	09/07/10	18
Chirurgia Generale, Hospital of Mantova	03/12/10	2
Clinica Chirurgica, "Careggi" Hospital, Florence	04/01/11	6
Chirurgia Generale, Hospital of S. Vito al Tagliamento	12/05/11	1
Total		**144**



Enrolment is proceeding quite well, with a constant trend.
The number of patients that each centre estimates to enrol is sufficient to guarantee the feasibility of the trial and, at present, only 1 centre has not yet randomized any patients and 5 centres stopped their accrual more than 5 months ago.
If the trend remains unchanged, the first interim analysis is planned for February / March 2012.



Patient characteristics

Data on baseline clinical and surgical characteristics are available respectively for 139 and 132 patients, and are well balanced between the two treatment arms.
About 80% of patients were randomized during surgery. The median age was 65 years, 57% of patients were male and 73% had previously received neo-adjuvant therapy. The mean distance of the tumour from the anal verge was 7.4 cm.
Laparoscopy was used in 11% of cases, 97% of the resections were curative (R0) and the mean distance of anastomosis from the anal verge was 4.5 cm. Details on patient characteristics, stratified by treatment arm, are shown in Tables 1 and 2.
Thirteen patients (10%) did not meet the eligibility criteria since a protective/temporary stoma was not performed (5 patients), or had undergone a Hartmann surgery (3 patients) or a handsewn coloanal anastomosis (5 patients).
Four patients randomized to receive the J-pouch reconstruction underwent a straight anastomosis. The feasibility of the colonic J-pouch, as assessed in patients in whom an anastomosis was carried out, is currently estimated to be 94%.

Table 1. *Clinical characteristics*

	Arm		
N (%)	**J-Pouch**	**Straight**	**Total**
Age			
mean (SD)	66.5 (8.6)	63.2 (10.7)	64.8 (9.9)
Gender			
M	40 (58%)	39 (56%)	79 (57%)
F	29 (42%)	31 (44%)	60 (43%)
ECOG			
0-1	56 (93%)	55 (85%)	111 (89%)
2-4	4 (7%)	10 (15%)	14 (11%)
Missing	9	5	14
cT stage			
2	13 (19%)	11 (15%)	24 (18%)
3	51 (76%)	56 (82%)	107 (79%)
4	3 (4%)	1 (1%)	4 (3%)
Missing	2	2	4
cN status			
+	31 (47%)	32 (52%)	63 (49%)
-	35 (53%)	30 (48%)	65 (51%)
Missing	3	8	11
cM stage			
+	1 (1%)	1 (1%)	2 (1%)
-	68 (99%)	69 (99%)	137 (99%)
Neo-adjuvant treatment			
CRT	44 (64%)	44 (63%)	88 (63%)
RT	6 (9%)	6 (9%)	12 (9%)
CT	1 (1%)	1 (1%)	2 (1%)
None	18 (26%)	19 (27%)	37 (27%)
CEA (n=115)			
mean (SD)	4.1 (6.7)	5.5 (9.4)	4.7 (8.1)
Tumour distance from anal verge (n=136)			
mean (SD)	7.1 (2.3)	7.6 (2.0)	7.4 (2.2)
Total	**69**	**70**	**139**

Table 2. *Surgical characteristics*

	Arm		
N (%)	**J-Pouch**	**Straight**	**Total**
Surgical approach			
Open surgery	57 (88%)	56 (84%)	113 (86%)
Laparoscopic	5 (8%)	10 (15%)	15 (11%)
Converted	1 (2%)	1 (1%)	2 (2%)
Combined	2 (3%)	0	2 (2%)
Tumour localization			
At the reflection	7 (11%)	9 (13%)	16 (12%)
Below the reflection	58 (89%)	58 (87%)	116 (88%)
Surgical resection			
Curative	62 (95%)	66 (99%)	128 (97%)
Not curative	3 (5%)	1 (1%)	4 (3%)
Bowel preparation			
SELG/PEG	26 (41%)	30 (46%)	56 (44%)
Other	37 (59%)	35 (54%)	72 (56%)
Missing	2	2	4
Status of the section rings			
Intact	57 (98%)	61 (97%)	118 (98%)
Interrupted	1 (2%)	2 (3%)	3 (2%)
Missing	7	4	11
Contour use			
No	27 (43%)	23 (37%)	50 (40%)
Yes	36 (57%)	40 (63%)	76 (60%)
Missing	2	4	6
Reconstruction technique			
J-pouch	59 (91%)	0	59 (45%)
Straight	4 (6%)	66 (99%)	70 (53%)
None	2 (3%)	1 (1%)	3 (2%)
Colon tract used			
Sigmoid colon	12 (21%)	15 (26%)	27 (24%)
Descendent colon	44 (79%)	42 (74%)	86 (76%)
Missing	9	10	19
Days of hospital stay (n=123)			
mean (SD)	11.7 (6.3)	10.3 (4.6)	11.0 (557)
Anastomosis distance from anal verge (n=123)			
mean (SD)	4.6 (1.9)	4.3 (1.6)	4.5 (1.8)
Total	**65**	**67**	**132**

Quality of life ancillary study

With increasing survival of patients with locally advanced rectal cancer undergoing multimodal treatment, the evaluation of long term results related to patient reported outcomes is clinically relevant. Such findings can be used to better inform the patient and address disease management.
The rectum removal, particularly when a TME is performed, determines several signs and symptoms, defined "anterior rectal resection syndrome", including fractionated defecation, urgency, incomplete defecation sensation and faecal incontinence. Factors causing the gravity and the incidence of such syndrome are the level of anastomosis, eventual anastomotic leak, reconstruction technique, sphincter damage caused by surgery or radiotherapy treatment, sympathetic denervation and the colon tract used for anastomosis.
The impact of the J-Pouch reconstruction on bowel function and quality of life has been widely studied highlighting that colonic J-pouch, with respect to straight, reduces the incomplete defecation sensation, the fractionated defecation and the evacuation time. However, with the J-pouch technique there is a potential increase of stypsis and, thus, the use of laxatives or evacuative enemas.
These results are based, however, on studies that included a small number of patients or used a retrospective design.
Moreover, bowel function was investigated with no standard, heterogeneous and often not validated self-reported questionnaires. These types of instruments make it difficult to compare studies worldwide and negatively affect the physician's ability to inform patients about the consequences related to their treatment for rectal cancer.
Therefore, for these reasons we felt it was important to evaluate, within a randomized and prospective study, bowel function and faecal incontinence using, for the first time, a validated questionnaire with acceptable psychometric properties.
The MSKCC questionnaire assesses bowel function using 3 scales (frequency, urgency/soilage and dietary) and 4 single items of clinical relevance. In order to detect problems related to constipation, we added 2 additional items so as not to alter its construct. Moreover, this will give us the opportunity to confirm and verify the properties of this instrument during post-operative follow-up.
It is also well-known that poor bowel function may have a negative effect on the perceived quality of life of patients and that this, in turn, can potentially affect treatment decisions.
To investigate this aspect too, we identified two questionnaires, the EORTC QLQ-C30 and the QLQ-CR38, which have strong psychometric properties, tested in numerous international clinical trials.
In addition to these tools, we aim to administer patients a questionnaire on sexual function, an important aspect usually not dealt with in depth particularly due to the difficulty in obtaining the information.

How to participate in the study

In order to enrol patients, it is essential you have written approval from your human research ethics committee. Once this has been obtained, a copy should be sent to the Clinical Trials and Biostatistics Unit, Istituto Oncologico Veneto of Padua, together with a copy of the commitment statement (attached to the study protocol) either by fax: 0039 049 82157-06 or e-mail: clinical.trial@ioveneto.it
Subsequently, your centre will be authorised to randomise patients and details of how to do so will be sent by email.

On 28th October, a conference will be held in Padua on the 'State of the art in the treatment of colorectal cancer and liver metastases'. During the lunch break, a meeting has been organized to which all participants of the J-Pouch study are invited to discuss the progress of the study and the possibility of carrying out other prospective studies.

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