

SEC-GISC_oR STUDY

Multicentric Study “Endoscopic Surveillance vs Surgery after *complete* polypectomy of a malignant polyp”

Rationale

- a) The 11th Recommendation of the New European Code against Cancer (3rd edition) says "Men and women aged 50 and over should be offered colorectal cancer screening. This should be within organized screening programs, with built in quality control procedures".
- b) All pathologists do not agree on the definition of “malignant polyp”, which has inevitable consequences on patient management.
- c) There is no consent on the best treatment after “complete” endoscopic polypectomy of a malignant polyp (there are no randomized trials comparing surgical radicalization and clinical follow-up).
- d) After “complete” endoscopic polypectomy, surgical resection plus lymphadenectomy is often performed with no pathological findings of disease (pT0 pN0).
- e) Sometimes patients are clinically followed after “complete” polypectomy and they present a disease recurrence after a time, with apparent therapeutic “delay”.
- f) In case of “complete” endoscopic polypectomy, there are no common, evidence-based guidelines to influence further choices, therefore treatment greatly vary in accordance to each Center or Physician personal opinion.
- g) The choice between surgery and clinical follow up is often based on scientifically-unproven clinical and pathological elements.

General design

This is a multicentric, prospective, observational, non-randomized study, therefore a patient’s allotment to either arm is exclusively a choice taken by the Clinician and Patient after adequate discussion.

The protocol has 2 arms (Appendix 1)

- ① Intensive follow up.
- ② Surgical resection plus lymphadenectomy.

In order to facilitate performing all follow up exams, it would be advisable to inform the patient’s General Practitioner of his/her enrolment in the study (see letter facsimile in Appendix 1).

Some patients allotted to the “surgical resection plus lymphadenectomy” arm may also be enrolled in the protocol “Predictive value of sentinel node in staging early-stage colorectal cancer (Stages I and II)”, based on the Center participation to both studies.

Inclusion criteria

- ❖ Histologically-diagnosed colorectal malignancy polyp after *complete* endoscopic resection (according to the endoscopist’s judgement) with histologically-confirmed free margins.

Exclusion criteria

- ❖ Malignant polyp after “incomplete” or “dubiously complete” resection (unconfirmed free margins).
- ❖ Familial adenomatous polyposis.

Stratification

Cases will be stratified by participating center and by surgical risk (ASA I-II vs ASA III and ASA IV; age < 75 y and age > 75 y; presence or absence of severe concomitant diseases).

Patients will also be stratified according to “high risk”* or “low risk”* of lymphatic spread from the excised malignant polyp.

Pathology quality control

Revision of the slides for all endoscopically-removed malignant polyps [slides will be sent for revision to Prof. M. Riso (Division of Pathology – Candiolo Cancer Center – Torino) or to Dr. A. Sonzogni (Division of Pathology – European Institute of Oncology – Milano)].

Definitions

Malignant polyp:

Polyp where adenocarcinomatous glandular cells have gone beyond the muscularis mucosae infiltrating the submucosa. According to TNM classification malignant polyps are staged pT1 cN0 cMo (Dukes’ stage A).

Malignant polyps may present nodal metastases (pT₁ p N₊).

Malignant polyps is synonymous with “early colorectal cancer”.

“Complete” polypectomy of a malignant polyp:

According to Haggitt’s criteria, a polypectomy of a malignant polyp can be considered “complete” when the pathology report satisfies the following requirements:

- resection margin certainly free of neoplastic invasion (>1 mm) in all correctly-oriented sections;
- non-G3 carcinoma;
- no evidence of vascular invasion (hematic and/or lymphatic).

“High risk” malignant polyp:

- grading G3;
- margin involvement < 1 mm;
- *sessile* malignant polyp;
- neoplastic involvement of Haggitt’s levels 3-4 in a *peduncolaed* malignant polyp (Gastroenterology, 1985).

“Low risk” malignant polyp:

- neoplastic involvement of Haggitt’s levels 1-2 in a *peduncolated* malignant polyp;
- grading G₁-G₂;
- no vascular spread (hematic and/or lymphatic);
- free margins of over 1 mm.

Tumor “Budding”:

- presence of isolated or clustered (less than 5 elements) carcinomatous cells in the struma of the tumor-spread margin;
- low grade (0-9 budding foci by 250x magnification) vs high grade (10 or more foci by 250x magnification).

“Microstaging”:

- ratio Adenomatous tissue/Adenocarcinoma: qualitative evaluation of the percentage of adenomatous tissue in ratio to carcinomatous tissue (lesions presenting little invasive carcinoma have a lower metastatic potential than polyps made up mostly by invasive carcinoma);
- level of peduncle invasion (superficial – mid – deep third; Haggitt’s levels) and of submucosa invasion in sessile malignant adenomas (sm1, sm2, sm3);
- microscopic measurement (micron) of the maximum depth and width of carcinomatous spread.

Among low-risk lesions, microstaging detects a subset of malignant carcinomas with a potential of nodal involvement next to zero: invasion depth <300 micron; invasion depth <2000 micron associated with maximum width <4000 micron with no tumor budding.

Procedure for data collection

An online procedure has been developed for data collection: from website www.ieo.it, click on “The GISCoR Studies” on the home page, then click on “Reserved area”. From there it is then possible to access the data collection form and insert patients’ data. In that area it is also possible to download a printable version of the data collection form.

The responsible physician for each participating Center has his Username and Password and a short instruction manual. Researchers will periodically receive a Report regarding accrued cases.

For any further information, please contact the **Organizing Secretariat:**

- Coordinators: Dr. B. Andreoni (bruno.andreoni@ieo.it) and Dr. C. Crosta (cristiano.crosta@ieo.it)
- Data Managers: Ms. A. Perilli and Ms. D. Tamayo (segreteria.studigiscor@ieo.it antonella.perilli@ieo.it; darina.tamayo@ieo.it).

**ENDOSCOPIC SURVEILLANCE vs. SURGERY
AFTER COMPLETE POLYPECTOMY OF A MALIGNANT POLYP**

GENERAL DESIGN

Multicentric, prospective, observational, non randomized study¹



INCLUSION CRITERIA:

Histologically diagnosed malignant polyp with free margins after complete endoscopic resection

Endoscopic surveillance with intensive follow-up

Surgical resection with lymphadenectomy²

STRATIFICATION:

- Surgical risk (ASA I-II; ASA III-IV)
- Age (<=75 aa; >75 aa)
- Severe concomitant diseases (Yes; No)
- Risk of lymphatic spread ("high risk" or "low risk" malignant polyp)

ESCLUSION CRITERIA:

- "Incomplete" or "dubious" resection of the malignant polyp(s)
- Family adenomatous polyposis

NOTE-1: Patients allotment to one of the two arms will be done on line after diagnostic evaluation of the general criteria for each treatment (see criteria form).

NOTE-2: Some patients undergoing surgery could be enrolled also in the SN-GISCoR study "Predictive value of sentinel node"

**ENDOSCOPIC SURVEILLANCE vs. SURGERY
AFTER COMPLETE POLYPECTOMY OF A MALIGNANT POLYP**

**FOLLOW-UP SCHEDULE ENDOSCOPIC SURVEILLANCE
FOR HIGH-RISK MALIGNANT POLYPS**

EXAMINATION	Month 0	Month 3	Month 6	Month 12	Month 18	Month 24	Month 36	Month 48	Month 60
CLINICAL EVALUATION*	X	X	X	X	X	X	X	X	X
CEA	X		X	X	X	X	X		X
ABDOMEN US/CT	X		X	X	X	X	X	X	X
ENDOSCOPY	X	X	X	X		X	X		X
ECHOENDOSCOPY (only for rectal polyps)**	X		X	X		X	X		X
CHEST X-Ray	X			X			X		X

** CLINICAL EVALUATION is mandatory, while all other examinations may be performed with a different schedule according to the clinician's judgement, as long as they are duly registered*

*** ECHOENDOSCOPY is optional (if necessary a pelvic CT/MRI can be performed instead)*

**FOR LOW RISK MALIGNANT POLYPS,
ENDOSCOPIC EXAMINATION IS ONLY REQUIRED AT 1-3-5 YEARS**

FOLLOW-UP SCHEDULE SURGERY ARM

**FOR TRANSANAL EXCISION
SAME FOLLOW UP AS FOR ENDOSCOPIC ARM**

**ypT0N0
ypT1N0
Dukes A**

ESAMINATION	Month 0	Month 6	Month 12	Month 18	Month 24	Month 36	Month 60
CLINICAL EVALUATION*	X	X	X	X	X	X	X
CEA	X	X	X	X	X	X	X
ABDOMEN US/CT	X		X				X
ENDOSCOPY	X		X			X	X
ECHOENDOSCOPY (only for rectal polyps)	X						
CHEST X-Ray	X						X

**ypT2-ypT1N+
Dukes B,C**

ESAMINATION	Month 0	Month 6	Month 12	Month 18	Month 24	Month 36	Month 60
CLINICAL EVALUATION*	X	X	X	X	X	X	X
CEA	X	X	X	X	X	X	X
ABDOMEN US/CT	X		X			X	X
ENDOSCOPY	X		X			X	X
ECHOENDOSCOPY (only for rectal polyps)**	X						
CHEST X-Ray	X		X			X	X

*** CLINICAL EVALUATION is mandatory, while all other examinations may be performed with a different schedule according to the clinician's judgement, as long as they are duly registered**

**** ECHOENDOSCOPY is optional (if necessary a pelvic CT/MRI can be performed instead)**

**ENDOSCOPIC SURVEILLANCE vs. SURGERY
AFTER COMPLETE POLYPECTOMY OF A MALIGNANT POLYP**

**ALLOTTED BY
THE COORDINATING CENTER**

EVALUATION Form

Center No:

Pt. No:

Initials: **Sex:** F M **Date of Birth:** / /

I- FAMILIARITY (for colorectal cancer – 1st grade): Yes No

II- CONCOMITANT DISEASES: Yes No if so, specify cardio-vascular respiratory
 renal/hepatic insuff. tumor _____
 IBD other _____

III- ASA: I II III IV

IV- SYMPTOMS:

Yes No if so, proctorrhagia stipsis other _____
 solid/liquid b.m. diarrhea

V- PREVIOUS COLONOSCOPIES:

Yes No Date (year last colonoscopy)

1.- Complete colonoscopy Yes No if not (specified site reached and causes) Site¹ Cause²

2.- Previous adenomas Yes No if so: single multiple

VI- PREVIOUS COLONIC RESECTION:

Yes No if so: Type³

Legenda:

¹Site: 1 rectum; 2 sigmoid c.; 3 descending c.; 4 splenic flex.;

5 transverse c.; 6 hepatic flex.; 7 ascending c.

²Cause: 1 inadequate evacuation; 2 manual difficulty;

3 bowel stenosis; 4 other

³Type: 1 right c.; 2 transverse c.; 3 left c., 4 ARR; 5 Miles

**ENDOSCOPIC SURVEILLANCE vs. SURGERY
AFTER COMPLETE POLYPECTOMY OF A MALIGNANT POLYP**

ALLOTTED BY
THE COORDINATING CENTER

ENDOSCOPY/PATHOLOGY FORM

Initials: **Sex:** F M **Date of Birth:** / /

Center No:

Pt. No:

Date Exam / / Performing clinician _____

I- Dug support: Yes No if so (specify drug and dose): _____

II- Complete colonoscopy: Yes No if not (specify reached site and causes): Site¹ Cause²

III- Visual-cleaning: optimal suboptimal scarce (no more than 20% of the mucosa hidden) inadequate (over 20% of the mucosa hidden)

IV- Procedure tolerance: neglectible pain mild pain severe pain

V- Complications: Yes No If so (specify date and type of occurrence)

- perforation Date / /
- bleeding, if so:
 - immediate delayed Date / /
 - other _____ Date / /

VI- Presence of NON malignant polyp Yes No

Polyp	Site ¹	Type ³	Dimension (mm)	Procedure ⁴	Histology ⁵
1	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="text"/>
2	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="text"/>

COMPLETE FOR MALIGNANT ADENOMA(S):

VII- Presence of malignant adenoma(s): Date Polypectomy / /

Adenoma CA	Site ¹	Type ³	Dimension (mm)	Electroresection ⁶	APC ⁷	Grading ⁸	Distance from res. margin (mm)	% of tumor	Invasion ⁹
1	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
2	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>

Legenda: ¹Site: 1 distal rectum; 2 medial r.; 3 proximal r./rectosigmoid j.; 4 sigmoid c.; 5 descending c.; 6 splenic f.; 7 transverse c.; 8 hepatic f.; 9 ascending c.; 10 caecum
²Cause: 1 inadequate cleaning; 2 manual difficulty; 3 bowel stenosis; 4 other ³Type: 1 sessile; 2 peduncolated; 3 non polypoid (flat)
⁴Procedure: 1 polypectomy; 2 biopsy ⁵Histology: 1 hyperplastic; 2 tubular, 3 tubulo-villous; 4 villous; 5 mixed aden; 6 serrated aden.; 7 inadequate; 8 normal; 9 other
⁶Electroresection: 1 single fragment; 2 piecemeal ⁷APC: 1 Yes; 2 No ⁸Grading: 1 G1-G2; 2 G3 ⁹Invasion: 0 none; 1 lymphatic; 2 vascular; 3 lymphatic/vascular

**ENDOSCOPIC SURVEILLANCE vs. SURGERY
AFTER COMPLETE POLYPECTOMY OF A MALIGNANT POLYP**

CRITERIA Form

ALLOTTED BY
THE COORDINATING CENTER

Center No:

Pt. No:

Initials: Sex: F M Date of Birth: / /

- **Informed consent to participate in the study**
- **Histologically diagnosed malignant adenoma with request for pathological revision** (the pathological revision is necessary for quality control during data analysis)
- **Complete removal** (according to the endoscopist's judgement confirmed by the pathologist)

I- CRITERIA ORIENTING TOWARDS ENDOSCOPIC SURVEILLANCE:

1- "**Low risk**" malignant adenoma completely removed:

- Grading G1-G2
- Margin over 1 mm from infiltration
- No lymphatic and/or vascular invasion of the peduncle
- Pedunculate polyp with infiltration limited to levels 1-2

2- "**High risk**" adenoma in high surgical risk patient (ASA IV; age over 75 y)

3- "**High risk**" adenoma in patient refusing surgery

II- CRITERIA ORIENTING TOWARDS SURGERY:

1- Presence of at least **one** of the following criteria for "**high risk**" malignant adenoma:

- Grading G3
- Infiltration less than 1 mm from the margin
- Lymphatic and/or vascular invasion of the peduncle
- Sessile polyp
- Infiltration of levels 3-4 (if peduncolated polyp)
- Piecemeal procedure

2- "**Low risk**" adenoma in patient requesting surgery

Patient allocated to arm:	I- ENDOSCOPIC SURVEILLANCE <input type="checkbox"/>	II- SURGERY <input type="checkbox"/>
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**ENDOSCOPIC SURVEILLANCE vs. SURGERY
AFTER COMPLETE POLYPECTOMY OF A MALIGNANT POLYP**

ALLOTTED BY
THE COORDINATING CENTER

SURGERY Form

Center No:

Pt. No:

Initials: Sex: F M Date of Birth: / /

I- Surgical procedure: Date of procedure: / /

I.I- Type of procedure: Laparotomic Laparoscopic

II- Type of resection (with lymphadenectomy): Right hemicolectomy Miles Procedure Segmentectomy
 Left hemicolectomy Anterior Rectal Resection
 Transversectomy TEM *

III- Pathology Report:

ypT ypN G Total nodes: Metastatic nodes:

Distant metastases Yes No if so (specify): _____

Resection margin: R0 R1

IV- Postoperative complications: Yes No

- | | | |
|---|---|--------------------------------------|
| <input type="checkbox"/> Major wound infection | <input type="checkbox"/> Intestinal occlusion | <input type="checkbox"/> Other _____ |
| <input type="checkbox"/> Sepsis | <input type="checkbox"/> Hemoperitoneum (bleeding from the drain) | |
| <input type="checkbox"/> Anastomosis dehiscence | <input type="checkbox"/> Perioperative death (within 30 days) | |

V- Hospitalization: (days)

***AFTER TEM ENDOSCOPIC FOLLOW UP IS APPLIED**

**ENDOSCOPIC SURVEILLANCE vs. SURGERY
AFTER COMPLETE POLYPECTOMY OF A MALIGNANT POLYP**

**ALLOTTED BY
THE COORDINATING CENTER**

FOLLOW-UP Form

Center No:

Pt. No:

Initials: **Sex:** F M **Date of Birth:** / /

Visit:
Month:

Check-up Date : / /

Patient Arm: **ENDOSCOPIC SURV.**
 SURGERY

I- ENDOSCOPIC EXAM: Date / /

Anastomotic recurrence Yes No if so (complete endoscopic treatment)

Recurrence on site of previous polypectomy Yes No if so (complete endoscopic treatment)

Biopsies Yes No

Endoscopic treatment Yes No if so: APC Polypectomy

Pathology report Flogosis / normal Severe dysplasia
 Adenomatous tissue Adenocarcinoma

II- ABDOMEN US: Date / / Liver metastases: Yes No Suspect

Possible CT: Yes No Date / / Liver metastases: Yes No Suspect

III- CEA: Date / / Value (please specify the Lab normality range) _____

IV- CHEST_XRay: Date / / Lung metastases: Yes No Suspect

Possible CT: Ye No Date / / Lung metastases: Yes No Suspect
s

V- USEndoscopy (only for rectal polyp): Date / / uT uN

INFORMED CONSENT FORM

Observational Multicentric study: "Endoscopic surveillance vs surgery after *complete* polypectomy of a "malignant polyp"

Dear Sir, Madam,

over the last few years screening exams on patients showing no or few symptoms, allowed to diagnose bowel cancer at a very early stage ("malignant polyps"). Their treatment leads in most cases to their complete cure.

However, at present it has yet to be established whether the best treatment after "complete" endoscopic polypectomy is a surgical "radicalization" procedure or simply clinical surveillance in qualified centers (as a "complete" polypectomy may be sufficient).

After adequate information by the Clinicians from the Center where the "complete" polypectomy was performed, you should decide with your attending Physician whether to undergo clinical follow up or surgical resection with lymphadenectomy, according to the study protocol which you can read, should you wish to do so.

This study was approved by the Ethical Committee of the Center and is endorsed by a number of Scientific Societies expert in the field. The study started in several Centers with proven experience in treating colorectal *malignant polyps*.

Whatever your decision, whether "surveillance" or "surgery", in case you agree to participate in the study, you will be invited for your first follow up in about 3 months.

You have the right to withdraw from the study at any given moment without giving any justifications.

Having read the information form, I had the chance to ask all the questions about the protocol that I deemed necessary and I accept to participate in the study.

Date _____

The patient

.....

The study investigator

I consent

I do not consent

that all my clinical information are given to my General Practitioner, Dr.

.....

the patient

.....

INSTRUCTIONS FOR DATA REGISTRATION SEC-GISCO_R

Summary

- Technical requisites
- Username and Password
- How to connect
- How to enter new cases
- How to modify entered data
- Virus/Privacy
- Failures

Technical requisites

1. Microsoft Windows system (no other system allowed).
2. Internet Explorer version 6 or higher (no other browser or lower versions allowed).
3. Interned connection (also via modem).

Question: how do I check which Internet Explorer version I'm using?

Answer: open Internet Explorer, menu “?”, “**information**”.

Q: I'm using Internet Explorer 5. what can I do?

A: Internet Explorer upgrading is free. If you have a fast internet connection you can download it from the Microsoft website (“**tools**”, “**Microsoft update**”), or please contact us (segreteria.studigiscor@ieo.it) and we'll send you a CD.

Q: Is Internet Explorer 6 enough? Is no other software necessary?

A: Yes, Internet Explorer 6 is the sole software necessary

Username and Password

In order to access the database username and password are necessary. To have one, please e-mail segreteria.studigiscor@ieo.it specifying your name and e-mail address.

NB username and password are as personal as your credit card code; they are needed to protect your patients' privacy as well as what you do.

How to connect

1. Open Internet Explorer,
2. Access www.ieo.it
3. Click on the top right corner “**The GISCo_R Studies**”
4. Click on “**Access area reserved for researchers**”
5. At the question “**You are accessing an area external to the site...**” click **OK**
6. At the question “**Protection notice. Information on this site cannot be seen or modified by othersContinue?**” click “**Yes**”
7. Type your username, password and database

How to enter new cases

1. Access the database (see previous paragraph).
2. Click on “**New record**”

3. Enter all data and save them by clicking on “**submit changes**”
4. Keeping a printed copy of the form is recommended. If your PC is connected to a printer, just click on “**print**” in the top right corner.

Q: What should I do when I don't have all data?

A: The database is very flexible. You can save the data you have and modify or complete them later

How to modify entered data

1. Access the database
2. Click on “**find records**” and type patient's date of birth or initials.
3. Click on Search
4. Double click on the case you have selected
5. Modify data as needed, then save by clicking on “**submit changes**”

Q: I accidentally cancelled a whole record. What can I do?

Q: I accidentally entered incorrect modifications in a record. What can I do?

A: No problem. If you have cancelled, overwritten and saved, contact us and we will manage to salvage your record.

Q: After I exit the database without saving by clicking “submit changes” can the data be salvaged?

A: Sorry, no. You'll have to reenter them.

Virus/Privacy

Q: I found a virus on my PC. What should I do?

A: The database is on a server operating via Linux system. All technical efforts to protect it from viruses, hackers, pirates, robbers, flooding, blackout, failures and fires have been made and are constantly upgraded. It is practically impossible for our server to get infected by a virus. It is also impossible for external users to infect the server. All data are coded and protected from the moment they leave your computer. Computer. All obligations required by law regarding data protection have been fulfilled.

Failures

If you have any problem, please feel free to mail segreteria.studigiscor@ieo.it. We will be happy to assist you in any way.

Version 2.0 26/04/2006 by manlioalerio

Having read the informed consent form from the European Institute of Oncology, I confirm that I have been given ample opportunity to discuss with all aspects of the study which I am about to undergo. The responsible physician is willing to give me any further information I may require in the future, either with me or, if I so wish, with my "external" attending physician.

I have been adequately informed about the aims and methods of the study and I hereby give my free and voluntary participation in the study. I also give my consent that my personal data be used for statistical purposes, in accordance to the law on the treatment of personal data.

I received a copy of the informed consent form.

Patient's signature

Date

Physician's signature _____

Witness's signature _____