# Post-operative diagnostic revision for Crohn Disease after subtotal colectomy for inflammatory bowel disease. Title: Diagnostic revision after sub-total colectomy

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# Original Research Article

# Post-operative diagnostic revision for Crohn Disease after subtotal colectomy for inflammatory bowel disease.

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**Short Title:** Diagnostic revision after sub-total colectomy

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**Abstract:**

Purpose: Subtotal colectomy (STC) is performed for severe acute and refractory colitis. The diagnosis can be difficult even after the surgery when colectomy specimen has overlapping features of Ulcerative Colitis (UC) and Crohn's disease (CD). The aim of this study was to evaluate the rate of post-operative diagnostic revision to CD after surgery and determine predictors factors.

Methods: Retrospective study of 110 patients who underwent STC (2005-2018).

Results: pre-operative diagnosis comprised: UC=80(73%), CD=11(10%) and Unclassified Colitis (IBDU=19, 17%). Initial diagnosis of IBDU and UC was modified to CD in 6 patients (6 %) after STC. The final diagnosis after the follow-up of 10±6 years switched from CD for 8 patients (9%). The multivariate analysis showed that patients with a colitis evolving for less than 10 years and initial diagnosis of IBDU were the two independent factors associated with an increased risk of diagnosis change to CD (p=0.03; p=0.016). At the end of the follow up 15 patients (14%) had a definitive stoma.

Conclusions: In patients with IBD, attention must be paid to determine the right restorative strategy to patients with an evolution of the disease less than 10 years or with IBDU who are more at risk to have a diagnosis change to CD after STC.

**INTRODUCTION:**

The spectrum of inflammatory bowel disease (IBD) encompasses both Crohn's disease (CD) and ulcerative colitis (UC). While UC affects solely the rectum and the colon, CD may be found throughout the gastrointestinal tract, including the rectum and colon in the case of CD.[1-5] In some cases, patients with chronic colitis clearly have IBD based on the clinical history but macroscopy and/or endoscopic biopsies show no definitive features of UC or CD; the term unclassified colitis (IBDU) is thus used for these patients. [6] Post-operative examinations of resections of such cases usually provide definitive evidence of UC or CD. The diagnosis can be difficult even after the surgery when colectomy specimen has overlapping features of UC and CD and, in those cases, pathologists use the term of Indeterminate Colitis (IC).

Accurately distinguishing between UC and CD is crucial as the surgical treatment for each differs considerably. While restorative proctocolectomy (RPC) is the usual approach in cases of UC[7-9], many surgeons are reticent to offer it to patients with CD.[10, 11] Indeed, pouch failure is frequently accompanied by an alteration of the original diagnosis from UC to CD.[12, 13] Therefore, strategies to minimise the need for post-operative revision of the diagnosis are critical.

There is a variety of indications for surgery in patients with colitis. The detection of dysplasia while the patient is under surveillance is observed most frequently in the setting of multiple biopsies, and prompts RPC.[14] However, surgery is also indicated in at least two other situations in which a long history and multiple biopsies are not always available: severe acute colitis and refractory colitis. These two situations now account for the majority of the indications for surgery.[15, 16] It is more likely that it in such cases diagnosis uncertainty is more frequent, resulting in increased rates of pouch failure after RPC.

The aim of this study was to evaluate the rate of diagnosis change and to identify predictors factors of diagnosis revision to CD for patients who underwent STC for severe acute colitis or refractory colitis.

**METHODS AND PATIENTS:**

This retrospective observational study reports a monocentric experience in the management of IBD requiring surgical treatment in an expert center for IBD, Saint Antoine Hospital in Paris. All patients who underwent STC at St Antoine's hospital between 2005 and April 2018 were included.

The diagnosis of colitis was based on a combination of clinical features, imaging modalities endoscopic findings, and histological interpretation of biopsies by pathologists expert in gastro intestinal pathology including IBD.

Severity of the colitis was evaluated with the Lichtiger's score.[17] Complicating factors including colectasia or colonic perforation were derived from CT scans and endoscopy was performed when clinically indicated. There is two frequent indications for STC in patients with IBD: first patients with severe acute colitis defined according to Truelove and Witts' criteria or a Lichtiger's score higher than 10 who were admitted acutely and who failed to respond to maximum medical treatment or who had developed complications as a result of their pathology (mostly sepsis, colectasia or haemorrhage), and required emergency surgical intervention. The second indication is for patients with refractory colitis defined as steroid-dependent colitis (inability to reduce steroids below the equivalent of prednisolone 10mg/day within 3 months or relapse within 3 months of stopping steroids) or steroid-refractory colitis (active IBD despite prednisolone up to 0.75 mg/kg/day for 4 weeks) or immunomodulatory-refractory colitis (active IBD despite thiopurines or mercaptopurine for 3 months).

STC was performed by laparoscopy or laparotomy.[18] Ileostomy was always created in the right iliac fossa. Sigmoidostomy was created either suprapubic in the midline incision or with the ileostomy depending on surgeon's choice.

After STC patients were reclassified as CD, UC, or IC either after pathological analysis, or either during the follow up according to the guidelines proposed by the European Society of Pathology and the European Crohn's and Colitis Organization.[6, 19] Pathological diagnosis of IC on resected specimens relied on the presence of clear evidence of IBD, with "overlapping features" or the absence of a "clear diagnostic pattern", with insufficient criteria to make a definite diagnosis of UC or CD.[6] Before STC some patients were considered to have an unclassified colitis (IBDU) as the diagnosis was only made on disease history and endoscopic findings. For these patients, no histology was available before STC. A decision to attempt restore intestinal continuity was made only after definitive pathology results were available.

## Statistical analysis

Descriptive analyses are presented as median (range) or mean ± standard deviation for quantitative data and as number of patients (percentage of patients) for categorical data. The correlation between diagnostic modification and initial diagnosis was studied by univariate analysis (chi-squared). All tests were two-sided, and a $p$ value $<0.05$ was considered to be significant. The multivariate analysis was performed using a backward stepwise logistic regression model that included all variables with a $p$ value $<0.1$ in univariate analysis.

**RESULTS:**

*Patients:*

One hundred and ten patients (mean age of 69±23 years) underwent STC for colitis. The mean time between the diagnosis of IBD and surgery was 10±6 years. Details of the patients can be

found in Table 1. STC was performed for severe acute colitis in 58 patients (53%), of whom 23 (40%) exhibited an acute complication related to their disease and for refractory colitis in the remaining 52 patients (47%). 61 (55%) patients had received corticosteroid treatment within 6 months of surgery, 69 (63%) had immunosuppressive therapy within 6 months, while 67 (61%) had been treated with monoclonal TNFα inhibitors.

*Diagnosis revision (Figure 1):*

The pre-operative diagnosis comprised UC (n=80, 73%), CD (n=11, 10%), and IBDU (n=19, 17%). The pathological analysis of the piece of STC allowed a rectification of the initial diagnosis for several patients. The previously IBDU cases (n=19, 17%) were reclassified mainly as UC (n=14, 74%), as CD (n=4, 21%) and IC (n=1, 5%). Among the patients initially diagnosed as UC (n=80, 73 %), 6 patients (8 %) had a change of diagnosis: 4 (5%) became IC and 2 (3%) CD. There was no change of diagnosis for patients initially diagnosed with CD.

Diagnosis modifications continued during the follow-up period of 10 years (±5 years), during which patients had their surgery to restore intestinal continuity.

Among the 80 patients initially diagnosed with UC, 69 (86%) didn't have a change of diagnosis at the end of the follow-up. Among the 19 patients initially diagnosed with IBDU only 1 patient stayed with an IC.

During the follow-up, 8 patients (9%) among those with UC and IC were deemed to have CD. At the end, compared to the initial diagnosis, 14 patients (14%) classified UC, IBDU or IC were found to be CD.

We performed an univariate analysis between the group of patients diagnosed with UC, IBDU or IC with a change of diagnosis to CD during the study and the patient who stayed with the initial diagnosis to determine predictors factors to be reclassified as CD. (Table 2) Patients with

a colitis evolving for more than 10 years had less risk to have a change of diagnosis to CD, p=0.035. Patients with an initial diagnosis of IBDU were more likely to have a change of diagnosis to CD, OR= 4.08 IC 95% [0.9937; 16.1628] p=0.026. In multivariate analysis those two criterias were also associated with an increased risk of diagnosis change to CD with respectively p=0.03 and p=0.016 with an OR=5.81 [1.62-18.54] for IBDU patients.

*Impact of diagnostic revision in the strategy of restoration of intestinal continuity:*

The restorative continuity strategy was mainly guided by the pathological analysis of the STC specimen but also by risks factors of poor functional result as age, anal incontinence and severe perineal lesions. (Figure 2)

Excluding patients who were lost to follow up (n=2) or who died during the study (n=2), at the end of the follow up of 10 years (±5 years), 15 patients (14%) had a definitive stoma.

Among the 11 patients with an initial diagnosis of CD, 3 (27%) had a definitive stoma including 2 who never had an attempt to restore continuity according to their will.

Among the 14 patients with a diagnosis change to CD, 2 (14%) had a definitive stoma at the end of the follow up and 3 patients had a temporary ileostomy more than one year for the management of their CD. There was no difference of rate of definitive stoma between those two groups, p=0.623.

Among the 72 patients with a UC from the beginning, 7 patients (10%) had a definitive stoma.

Retrospectively, all histological samples of patients deemed to have CD were reanalysed to determine if features of CD existed. Details of those patients are given in supplementary table 1.

**DISCUSSION:**

Diagnostic revision after surgical treatment of UC is a quagmire for physicians. Many patients seek a RPC with the hope that they may be rendered stoma free. However, a resurgence of symptoms may prompt a reclassification of the diagnosis. The ileal pouch and the perineum are the most frequent sites of disease, which can lead to the construction of a diverting stoma which may become a permanent fixture. If the diagnosis had been accurate initially, the patient may have been spared restorative surgery, with the associated risks and dashed hopes. Even if one argues that an ileal pouch in the setting of CD may be appropriate in some cases, prior knowledge of the presence of CD would alter post-operative management and would colour both patient and clinician expectations.

Indications for surgery in UC can be divided into four categories: functional, prophylactic for cancer, resistance to treatment, and acute complications. Surgery for functional reasons and cancer prevention is most commonly seen in the context of a long disease history. In these cases, uncertainty over the diagnosis is unlikely. On the contrary, in the case of treatment resistance and especially in case of acute colitis and acute severe complications, the disease history may be short, with a corresponding increased risk of diagnostic revision after surgery. In the present series, the delay between initial diagnosis and STC was only 6.5 years, which is quite short for a chronic disease. The aims of this study were then to evaluate the diagnostic revision rate to CD after pathologic examination of the specimen obtained after STC and the one observed after surgery to restore intestinal continuity and during the follow up with endoscopic biopsies.

In our series, before surgery 19 patients were considered to have IBDU. This must be regarded as a different entity to IC. An unclassified designation may result from a lack of material for pathological examination. In the absence of specific features of CD, a definitive diagnosis may prove elusive. If these patients had been deemed to have IC, and underwent subsequent RPC, 4 patients with CD, and one with an IC would have undergone pouch surgery. It can be argued

that in the present series, 2 patients (14%) among the 14 who were considered to have UC after STC, while previously unclassified, ultimately were found to have CD. Same results are found in the literature as Zaghiyanand al.[20] However, when comparing diagnostic revision rates between patients who had UC either after being consider to have one or an unclassified one, there was no difference. Moreover, the long-term diagnostic modification rate in these two situations is within the ranges reported in the literature. In fact, the risk of diagnostic modification was significantly higher among patients who had their initial diagnosis modified and especially among those who had their diagnosis modified from UC to IC. In this specific group of patients, the rate of secondary diagnostic modification reached 25%. Such a rate is higher than the one observed in cases of IC in the literature.[21-26] With this finding in mind, should these patients have had an operation other than restorative proctocolectomy? Probably not, as ileorectal anastomosis in CD is not always accompanied by a good result, and RPC is offered to only highly selected patients. Thus, those patients with a modified diagnosis of IC, after previously being classed as UC, are more likely to fulfil the criteria of a CD patient who would be considered for RPC.[11, 12] In the present series, one patient with CD underwent RPC without disease recurrence at the last follow up.

The term IC is used to describe colitis without a clear argument for UC or CD after colectomy, in our series the frequency was 5% just after STC and 4% after follow-up. These rates are rather low compared to those found in the literature between 3% and 10%. [27] In our series, patients reclassified during the follow-up were patients with CD. In our study 14 patients (13%) classified UC, IBDU or IC were found to be CD after pathological examination of the piece of resections or during the follow up with the occurrence of perineal lesions or ileo-vaginal fistula. Seven of them (50%) had a restorative protectomy and 4 (43%) developed severe complications of the ileal pouch witch required a diverting stoma for several years. These complications highlight the importance of a good classification of the IBD in the strategy of restorative

continuity as shown in the study of Netz et al, the long-term quality of life for these patients is lower than in case of IRA. Taking into account the clinical impact, we analyzed individually the characteristics of the patients whose diagnosis was finally changed for CD: few studies have analyzed precisely the histological data of these patients, the Japanese study of Matsui et al. analyzed these features in their series of 735 patients with IBD with 23 patients whose diagnosis was modified (3%): patients initially UC whose diagnosis was rectified during follow-up for CD (n=8, 10%) have been done only after the detection of granulomas on biopsy material, the initial diagnosis of UC was based mainly on the diffuse appearance of colitis and the lack of cobblestones. In our series we have rectified the diagnosis of CD rather on a panel of histological arguments rather than on the exclusive presence of granulomas according to a methodology closer to the study of Henriksen and al. whose results are comparable to ours.[28] The univariate analysis realized, confirmed by an multivariate analysis to determine predictive factors of modification of the diagnosis found that disease evolution duration of less than 10 years and the diagnosis of IBDU were associated with an increased risk of modification of the diagnosis toward CD. This result enlightning the fact that for patients with a recent onset of the colitis, it might be necessary to take time to choose the right reconstruction strategy.

The confirmation of the original diagnosis by pathologic examination of the specimen obtained at STC allows the choice of subsequent appropriate surgeries, while particular heed needs to be paid to patients who have had a diagnosis of UC modified to IC after STC.

**Statements**

**List of collaborators of the Saint Antoine IBD Network:** Lionel Arrivé, Laurent Beaugerie, Anne Bourrier, Marine Camus, Najim Chafai, Edouard Chambenois, Ulriikka Chaput, Clotilde Debove, Charlotte Delattre, Xavier Dray, Jean-François Fléjou, Guillaume Le Gall, Nadia Hoyeau, Julien Kirchgesner, Cécilia Landman, Jérémie H. Lefèvre, Philippe Marteau, Chloé Martineau, Laurence Monnier-Cholley, Isabelle Nion-Larmurier, Violaine Ozenne, Yann Parc, Philippe Seksik, Harry Sokol, Magali Svrcek, Emmanuel Tiret.

**Declarations**

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**Author contribution:**

- Study conception: JHL, LB, YP
- Data acquisition: HH, MS, NC
- Analysis of data: HH, JHL, MS, NC
- First draft writing: HH, JHL, CS, MS, LB, YP
- Manuscript correction: All authors
- Final approval: All authors

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**Figure legends**

**Figure 1.** Evolution of the diagnosis.

STC: Subtotal Colectomy

**Figure 2.** Digestive continuity strategy after STC.

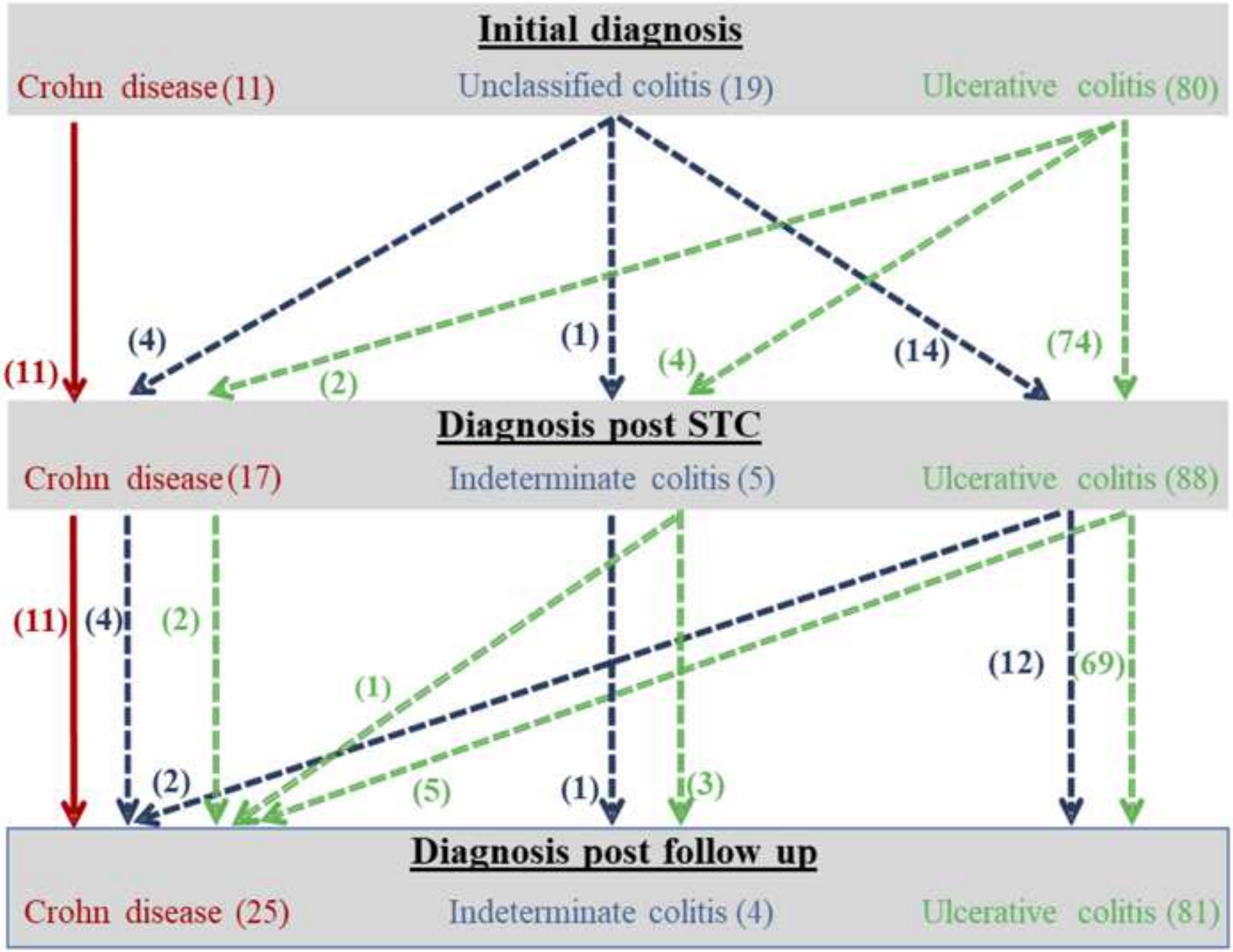
STC: subtotal colectomy; IBD inflammatory Bowel Disease; IBDU inflammatory Bowel Disease Unclassified; CD: Crohn’s disease; UC: ulcerative colitis; RPC: Restorative Proctocolectomy; IRA: ileorectal anastomosis; DS: Definitive Stoma; TS: Temporary Stoma; LTFU: Lost To Follow Up; APR: Abdomino-Perineal Resection

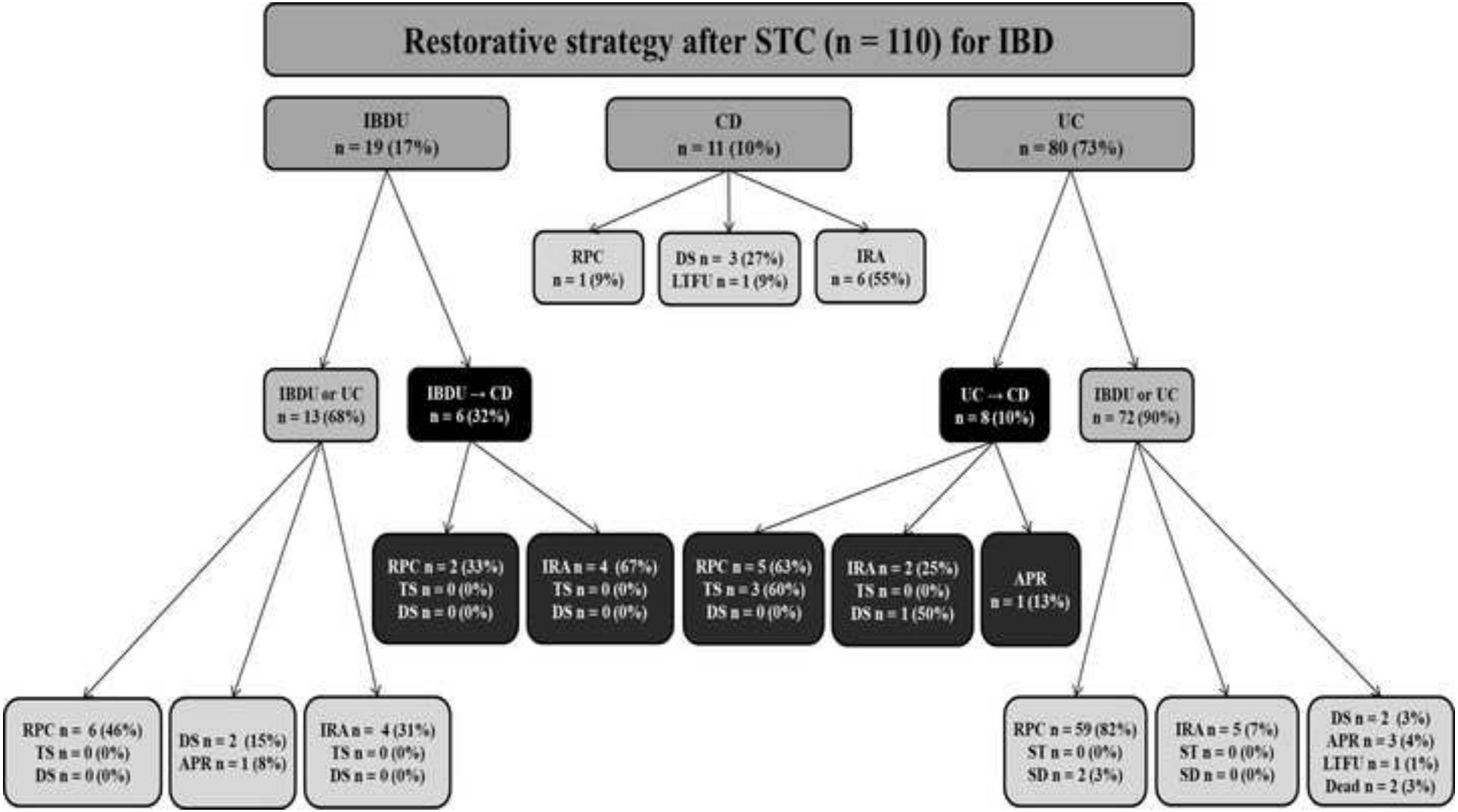
**Table 1.** Patients' characteristics before STC and indication for surgery

| **Characteristics** | **N (%) or Average ± SD** |
|---|---|
| Women | 44 (40%) |
| Age(y) | 69 ± 23 |
| BMI (Kg/m2) | 20±2 |
| Active Smoker | 21 (19%) |
| ASA score | |
| 2 | 85 (77%) |
| 3 | 17 (15%) |
| 4 | 2 (4%) |
| Age at diagnosis of IBD (y) | 57 ± 15 |
| Time between diagnosis and STC (y) | 5 ± 3 |
| **Preoperative diagnosis** | |
| Crohn's disease | 11 (10%) |
| Ileitis | 5 (46%) |
| Anoperineal lesion | 8 (73%) |
| Ulcerative colitis | 80 (73%) |
| Back wash ileitis | 3 (4%) |
| Unclassified colitis | 19 (17%) |
| **Indications for surgery** | |
| Emergency | 58 (53%) |
| Severe acute colitis | 35 (60%) |
| Toxic Dilatation | 7 (12%) |
| Sepsis | 11 (19%) |
| Haemorrhage | 5 (9%) |
| Refractory colitis | 52 (47%) |
| With dysplasia | 7 (13%) |
| Lichtiger's score | |
| ≤8 | 21 (19%) |
| 8<lichtiger≤10 | 16 (15%) |
| 10<lichtiger≤12 | 27 (25%) |
| >12 | 46 (42%) |
| **Treatment at time of surgery** | |
| Steroid prescription | 100 (91%) |
| ≤ 6 months | 61 (61%) |
| 6 months ≤ ≤ 1 year | 12 (12%) |
| ≥ 1 year | 21 (21%) |
| Dose of steroids (PO prednisone equivalence in mg) at time of surgery | 40±14 |
| Intravenous steroid before surgery | 45 (41%) |
| Immunosuppressive therapy within 6 months | 69 (63%) |
| TNF inhibitors within 6 months | 67 (61%) |

**Table 2.** Univariate analysis of demographics and pre-operative characteristics of patients with initial diagnosis of UC or IC with a change of diagnosis for CD compared to patients who stayed UC or IBDU.

| **Characteristics** | **Patients UC or IC without change of diagnosis n= 85** | **Patients with a change of diagnosis to CD n= 14** | **Univariate analysis p=** | **Multivariate analysis p=** |
|---|---|---|---|---|
| Age<40 years at the time of STC | 49 (58%) | 11 (79%) | 0 .237 | |
| Male gender | 50 (59%) | 7 (50%) | 0.571 | |
| BMI≥30 | 2 (2%) | 1 (7%) | 0.319 | |
| Active Smoker | 16 (19%) | 3 (21%) | 1 | |
| ASA score ≥3 | 15 (18%) | 1 (7%) | 0.246 | |
| Age at the time of diagnosis > 20y | 66 (78%) | 8 (57%) | 0.18 | |
| Time between diagnosis and STC ≤10y | 62 (73%) | 14 (100%) | 0.035 | 0.003 |
| **Preoperative diagnosis** | | | | |
| UC | 72 (85%) | 8 (57%) | 0.026 | 0.016 |
| IBDU | 13 (15%) | 6 (43%) | | |
| **Indications for surgery** | | | | |
| Emergency | 43 (51%) | 10 (71%) | 0.247 | |
| Refractory colitis | 42 (49%) | 4 (29%) | | |
| **Treatment at time of surgery** | | | | |
| Use of steroids within 6 months | 53 (62%) | 7 (50%) | 0.393 | |
| TNF inhibitors | 52 (61%) | 7 (50%) | 0.558 | |





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