Socioeconomic Impact of Emergency Therapies for Colorectal Cancer

3

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3.1 Global Socioeconomic Considerations

Colorectal cancers (CRC) are the third most common malignant tumors worldwide, and they are associated to an increased economic expenditure for healthcare systems due to its high diagnostic, therapeutic, and follow-up costs [1]. Disbursements per patient with CRC over a 5-year period of up to €39,607 (ranging from €33,300 to €49,900) have been estimated using year 2008 values [2], and a rough estimate of the economic burden for colorectal cancer worldwide was to be around USD 14–22 billion [3]. Despite that an elective surgical resection is the gold standard for CRCs curative treatment, up to 30% of CRC patients are presenting as a surgical emergency [4–6]. Emergency surgery for CRC increases postoperative morbidity, mortality, hospital stay, and costs [4, 5, 7]. Curative resection rate is significantly lower, with higher rates of ostomy formation within patients undergoing emergency surgery. Both 5-year overall and cancer-specific survival have been shown impaired for emergency CRC patients compared with those receiving elective procedures [6].

There is substantial heterogeneity in the methodologies and quality of the published economic evaluations of CRC at an elective setting, and only few are specifically focusing the emergency scenario; therefore, the true economic costs of emergent CRC are yet to be fully defined. The main costs of CRC are related to treatment (90%), compared with diagnostic and follow-up costs. Within all the

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stages, stage I would be the least costly and stage III the most expensive [8]. Those latest patients would present 25% more management-associated costs than those presenting as stage IV. For stage I patients, costs are relatively lower for the treatment (78%) and higher for the follow-up (14.8%) phases [2]. For stages II and III, total costs are mainly influenced by the cost of chemotherapy and biologics, the duration of the treatment with biological agents, and cancer recurrence rates. For stage IV patients, the use of biological agents and chemotherapy presented major impact on costs [2]. Regardless of the stage at diagnosis, primary tumors located at the rectum are most costly than those located at the colon, in all diagnosis, treatment, and follow-up phases of patient's management.

There is a high incidence of emergent presentations (30%) of CRC, which are associated with adverse postoperative and long-term outcomes. Patients receiving surgery after elective admissions had significantly lower adjusted odds of mortality compared with emergent patients, and mean hospital length of stay for elective patients is significantly lower than emergent ones [4, 5]. Thus, increased hospital resources would be required after an important percentage of the total CRC surgeries. Also, the costly treatments needed after the potentially higher recurrences observed for emergency cases could be critical for total expenditures [9]. Finally, increased costs are related to locally advanced and metastatic diseases that, compared to the other stages, are relatively more frequent presented as emergencies than in elective setting [2, 6, 10]. As a result, emergency surgeries for CRC may represent an underestimated cost burden to healthcare systems and society worldwide. Novel strategies for separately evaluate, reduce, and improve the quality of this emergent surgical procedures for CRC should be explored as a global health target.

3.2 Surgical and Long-Term Costs for Healthcare Systems

3.2.1 Types of Costs

Direct costs: Generated by healthcare utilization, they include:

- Hospital and intensive care unit admission periods
- Diagnostic procedures (at presentation and follow-up)
  - Laboratory and radiological investigations
  - Endoscopic exploration and stenting
  - Biopsy and histopathologic evaluation
- Therapeutic procedures
  - Surgical procedure(s) (operating room charges, instrumental)
  - Medication (analgesics, antibiotics, anesthetic drugs, blood transfusion)
  - Chemotherapy, radiotherapy, and biological therapy
  - Other (invasive lines, syringe pumps, physiotherapy, etc.)

- Visits to primary and paramedical healthcare providers after discharge
  - Outpatient visits
  - Wound and stoma care
  - Best supporting care
- Non-medical costs: Generated by expenses for travel to and from healthcare providers

At emergency presentation of CRC, surgery is usually performed immediately following the diagnosis, and as a result, the cost of this and the first required hospitalization would constitute more than 80% of the total direct costs.

Indirect costs: Generated by the impaired ability to work

- Loss of productivity
- Disability allowances
- Out-of-pocket costs to caregivers

Social impairment should also be taken into consideration in those patients and relatives. Quantifying and evaluating the social costs would be mandatory for assessing the real cost-effectiveness of the strategies applied for emergency CRC treatment.

3.2.2 Surgical Costs

Haider et al. identified 162,442 patients undergoing colonic resection for neoplasms, 48,599 at emergency setting, using Nationwide Inpatient Sample (NIS) data between 2001 and 2010 in the USA. The surgical procedure performed as an emergency had a mean cost of USD 22,616.33 per patient, USD 7813.53 more expensive than elective colonic resection in the same population (53% increase) [4]. Shah et al. used a database of CRC patients underwent surgical procedures separating those presenting with a diagnosis requiring emergency surgery (including bowel perforation, peritonitis, or obstruction). Patients receiving emergency surgical procedures spent 51.9% more admission days, produced hospital charges 68.3% higher, and had a nearly four times greater chance of in-hospital death than those who did not [5].

The influence on the total costs produced by the use of laparoscopy has been scarcely evaluated for CRC emergency resections. Koh et al. performed a study over patients who had undergone either emergency laparoscopic or open colectomies for various surgical conditions (i.e., lower gastrointestinal tract bleeding, colonic obstruction, and perforation). Matching was performed for age, gender, surgical diagnosis, and type of surgery. There were no significant differences between the groups for perioperative complications and length of stay. The cost analysis neither demonstrated any significant differences in the total, procedural, and the non-procedural costs between the two groups [11].

3.2.3 Long-Term Costs

Long-term costs for CRC are increasing, mainly associated with the high cost impact of biological agents. For locally advanced tumors, the total costs critically depend on the cost of chemotherapy and biological agents and recurrence rates [2]. Treatment costs for metastatic CRC are substantial, and a new trend for its increasing caused by the rising cost share of biologics has been observed [12]. Disbursements per CRC patient over a 5-year period of up to €39,607 (ranging from €33,300 to €49,900) were estimated using year 2008 values [2]. Moreover, the costs of continuing and advanced care phases would represent between 16.9% and 58.3% of the total long-term costs, depending on CRC stage [8]. In middle-adulthood CRC patients, working patients can expend nearby 3 months out of their employ. A study showed that factors associated with work resumption were, among others, stoma placement, postoperative complications, length of hospital stage, and receiving adjuvant treatments [13]. CRC represented in Spain, during 2011, the loss of 202,784 working days [14].

3.2.4 Reducing the Burden of Emergency Therapies for CRC

Self-expandable metallic stent (SEMS) placement as a bridge to elective surgery for left-sided malignant colonic obstruction appeared as an alternative to the traditional emergency surgical approach. A recent meta-analysis including 8 RCT found a significant lower risk of presenting postoperative complications, and undergoing temporary or permanent stomas, in patients treated with SEMS [15]. Other studies have evaluated the economic impact derived by the use of stenting on emergency setting compared to respective surgery. They showed, together with lesser postoperative morbidity, mortality, and stoma placement rates, decreased costs for patients receiving SEMS preceding elective surgery for the treatment of acute malignant left-sided obstruction [16, 17].

Screening for CRC can avoid an emergency presentation as allows to identify abnormal growths before the cancer development. Consequently, emergency CRC resection is frequently related to a failure of the screening. There is high disparity between countries and continents regarding the recommended screening timing for CRC. Also, several methods are currently available for CRC diagnosis at an asymptomatic phase including stool-based (occult blood, DNA panel), endoscopic, and radiological tests. Although the optimal strategy remains a matter, preventing emergency surgery through the development, promotion, and excellence of CRC screening allows the chance to save and improve lives, and also to save costs [4].

The Guidelines of the American College of Physicians (ACP) recommend [18]:

- To perform individualized assessment of risk for CRC in all adults.
- To screen for CRC in average-risk adults starting at the age of 50 years and in high-risk adults starting at the age of 40 years or 10 years younger than the age at which the youngest affected relative was diagnosed with colorectal cancer.

– To use a stool-based test, flexible sigmoidoscopy, or optical colonoscopy in patients who are at average risk and optical colonoscopy in those who are at high risk. Selection of the test should be based on patient preferences and the benefits and harms and availability of the test.
– To stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years.

Other potential solutions for reducing the increased costs associated to emergency presentation of CRC have been proposed, as the creation of dedicated emergency general surgery services. Increased rates of inpatient colonoscopies and definitive surgical procedures on the same admission have been observed after its introduction [19]. Moreover, the development of enhanced recovery pathways and bundles of evidence-based care, such as the proposed for emergency laparotomy, have been shown to improve the postoperative outcomes. The emergency laparotomy pathway quality improvement care (ELPQuiC) consists on the initial assessment with early warning scores, an early antibiotic therapy, less than 6-h time interval between decision and operation, goal-directed fluid resuscitation, and optimal postoperative intensive care [20].

3.3 Quality of Life After Emergency Therapies for CRC

3.3.1 Assessing the Quality of Life After CRC Emergency Surgery

The quality of life of individual patients undergoing both elective and emergency surgical interventions for CRC is crucial when evaluating the full socioeconomic impact of the disease. The World Health Organization define health-related quality of life (HRQOL) as the level of well-being and satisfaction associated with an individual's life and how this level is affected by disease, accidents, and treatments. The predictors of a HRQOL after colorectal surgery involve the impaired physical and social functions, ability to work productively, and the existence of specific symptoms [21]. When managing emergency CRC patients, who usually present with advanced stages, strategies aiming to improve HRQOL are essential. HRQOL evaluation allows to study the impact of disease on survivors and also to elucidate the optimal treatment when two interventions are similar in terms of survival [22].

There have been described multiple instruments for the assessment of HRQOL that could be useful for patients after CRC resection [Table 3.1]. The most frequently used are psychometric questionnaires that could be generic or disease-specific:

- Generic instruments
  – Nottingham Health Profile [23]
  – MOS Short Form 36 (SF-36) [24]
- Cancer-specific instruments
  – Functional Assessment of Cancer Therapy-General (FACT-G) [25]
  – European Organization for the Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [26]

Table 3.1 Instruments to measure HRQOL in colorectal cancer surgery

Generic	Cancer-specific	CRC-specific	Stoma patients	Functional status
NHP	FACT-G	FACT-C	mCOH-QOL	FIQL
SF-36	EORTC QLQ-C30	EORTC QLQ-CR38	Stoma-QOL	Wexner FIS
SF-6	QoL-CS	EORTC QLQ-CR29	Stoma care QOL index	LARS score
EQ-5D		FCSI		MSKCC BFI
SIP				
6MWT				
QoR-40 and -15				

Nottingham Health Profile (NHP), Short Form 36 (SF-36), 6-Item Short Form Health Survey (SF-6), EuroQol-5 dimension (EQ-5D), Sickness Impact Profile (SIP), 40-item Quality of Recovery Score (QoR-40), 15-item Quality of Recovery Score (QoR-15), 6-minute walk test (6MWT), Functional Assessment of Cancer Therapy-General (FACT-G), European Organization for the Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30), Quality of Life–Cancer Survivors (QoL-CS), Functional Assessment of Cancer Therapy–Colorectal Cancer (FACT-C) NCCN/FACT CRC Symptom Index (FCSI), Modificate City of Hope Quality of Life Ostomy Questionnaire (mCOH-QOL), Fecal Incontinence Quality of Life (FIQL), Fecal Incontinence Score (FIS), Memorial Sloan Kettering Cancer Center (MSKCC) Bowel Function Instrument (BFI)

- Colorectal cancer-specific questionnaires
  - Functional Assessment of Cancer Therapy-CRC (FACT-C) [27]
  - QLQ-CR38 [28]
  - QLQ-CR29 [29]

Generic tools allow to compare HRQOL between different diseases, but they are less specific for cancer patients. For CRC patients, an overall, generic instrument comprised of multiple dimensions, supplemented by a disease-specific subscale, has been proposed as the best approach to evaluate HRQOL [22].

3.3.2 Recovery After Colorectal Emergency Surgery

Postoperative recovery not only consists on the restitution of the previous physiological parameters, as social recovery should be also taken into account. Patient's recovery after surgery has then to be considered from a multidimensional perspective. It is divided between early and late periods and comprises psychological and functional recovery, adverse symptomatology, and personal satisfaction [30].

Enhanced recovery after surgery (ERAS) protocols have been developed for colorectal surgery patients aiming to reduce physiological stress and postoperative organ dysfunction through optimization of perioperative care and recovery. They require a multidisciplinary approach in all perioperative phases and appear to reduce times for bowel function recovery and to return to normal activities. ERAS protocols have been applied with safety and effectiveness at emergency colorectal

surgery setting, but its use is far to be widespread [31]. Due to the potential benefit for selected patients undergoing emergency operations, development and implementation of specific ERAS protocols after colorectal emergency surgery should be considered.

Late functional complications after CRC emergency surgery have increased together with the improvements on surgical technique and perioperative care that increased the primary anastomosis rates avoiding stoma placements. Those functional problems are more frequent during the first year after surgery. They include fecal incontinence, diarrhea, and constipation, together with frequency, urgency, and difficult evacuations. Those potentially postoperative adverse events should be considered before surgery and thus taken into account at decision-making process during the surgical intervention. Functional problems also depend on the previous patient's status, the surgical procedure performed, and perioperative morbidity. Extensive resections (i.e., subtotal colectomy) may increase bowel dysfunction rates; restricted postoperative social activity is more frequent in ileo-rectal or ileo-sigmoid anastomosis compared with segmental colectomies [32]. Diarrhea has been shown to be more common after right than left hemicolectomy, if less than 16 cm of the sigmoid colon remains, or if more than 10 cm of the terminal ileum is resected [33].

Incontinence are measured usually with the Fecal Incontinence Quality of Life (FIQL) and the Wexner Fecal Incontinence Score (FIS) [34]. The conservative treatment of fecal incontinence would consist on fiber and constipation agents. Surgery is reserved after its failure. The best invasive technique depends on the stage of the disease and patient's anatomy. Sphincteroplasty, sacral nerve stimulation, artificial bowel sphincters, and fecal diversion are the main options. Diarrhea (often associated to incontinence) is usually treated with opioid agonist (e.g., loperamide).

Low anterior rectal resections are lesser performed at emergency setting, but up to 80% of the patients develop bowel dysfunction postoperatively. Despite that the majority of functional impairments improve during the 6–12 first months, symptoms could persist up to 15 years after the surgical resection [35]. The symptoms are included under the term "low anterior resection syndrome" (LARS): fecal urgency, bowel fragmentation, frequent bowel movements, emptying difficulties, incontinence, and increased gas. To assess the severity of LARS, LARS score and the Memorial Sloan Kettering Cancer Center (MSKCC) Bowel Function Instrument (BFI) can be used [36, 37]. The factors associated with the development and severity of LARS are concomitant colonic dysmotility, neorectal pouch dysfunction, and damage to anal sphincter or pelvic nerves [35]. Together with dietary changes and pharmacologic therapies, pelvic floor rehabilitation and sacral nerve stimulation procedures are nowadays in use for the treatment of LARS.

Anastomotic stricture could cause bowel dysfunction in up to 22% of the patients undergoing colorectal resections [38]. Conservative treatments are the first step, including dietary changes and medical therapies. The invasive procedures for the management of postoperative anastomotic strictures include endoscopic balloon dilation, insertion of self-expandable metal stents, endoscopic incisional therapies, and surgery.

3.3.3 Impact of Stoma Formation

Stomas are commonly performed in emergency CRC surgery. Ileostomies or colostomies are widely used for either colonic diversion or decompression. They could be temporary or permanent, also end or loop. Diverting loop ileostomy is used after an emergency low anterior resection with colorectal anastomosis, and in patients with obstructing distal cancer. If feasible, it seems preferable over performing a loop colostomy in such cases, as loop colostomy has more risk of prolapse and sepsis. Ghost ileostomy is a primary anastomosis accompanying pre-staged ileostomy that could be externalized and opened at emergency surgery after a primary anastomotic leak. End colostomies are the most frequent stoma performed in emergency CRC surgery. Its formation could be difficult in obese patients, and they have increased risk for stoma necrosis. Complication rates following stoma formation range between 21% and 70% [39]. They are divided into early (within the first 30 days after surgery) and late complications. Emergency surgery, together with higher body mass index have been observed as a predisposing factors for stoma complications [40].

3.3.3.1 Early Complications

- *Improper stoma site selection* is the most commonly preventable complication of stoma surgery (36). Even in emergency situations, the stoma location should be marked before the interventions, being the surgeon the main responsible (Fig. 3.1a).
- *Dehydration* occur in up to 20% of ileostomy patients, and the risk is higher within the earliest postoperative days [39]. Excessive stoma losses can also lead to other late complications as electrolyte abnormalities, vitamin deficiencies, and malnutrition [41].
- *Stoma retraction* (1–17%) is more common in obese patients and emergency operations [40, 41]. If the stoma retraction develops into complete mucocutaneous separation, it could also lead to peritonitis (Fig. 3.1b).
- *Stoma necrosis* (13%) is also more frequent in obese patients, emergency surgery, and colostomies [42]. Necrosis is secondary to an excessive tension at the mesentery, excessive devascularization, or narrowly spaced sutures. Venous outflow impairment will turn the stoma purple-colored, but the wall is usually viable finally. In contrast, if the arterial inflow is compromised, full-thickness necrosis is presented, and when extension to the fascial layer is noted, surgical revision is mandatory (Fig. 3.1c, d).
- *Peristomal skin irritation* (3–42%) is a common complication more frequent with ileostomies than colostomies. Protruding ileostomies decrease their apparition and severity (Fig. 3.1e).
- *Parastomal infections and abscesses* are uncommon and mostly seen after stoma revision surgery (Fig. 3.1f).

3.3.3.2 Late Complications

- *Parastomal herniation* incidence range between 0% and 48%, being higher for end stomas and for colostomies [40, 41]. The risk factors include obesity, poor nutritional status, site of the wall incision, and emergency surgery. Parastomal

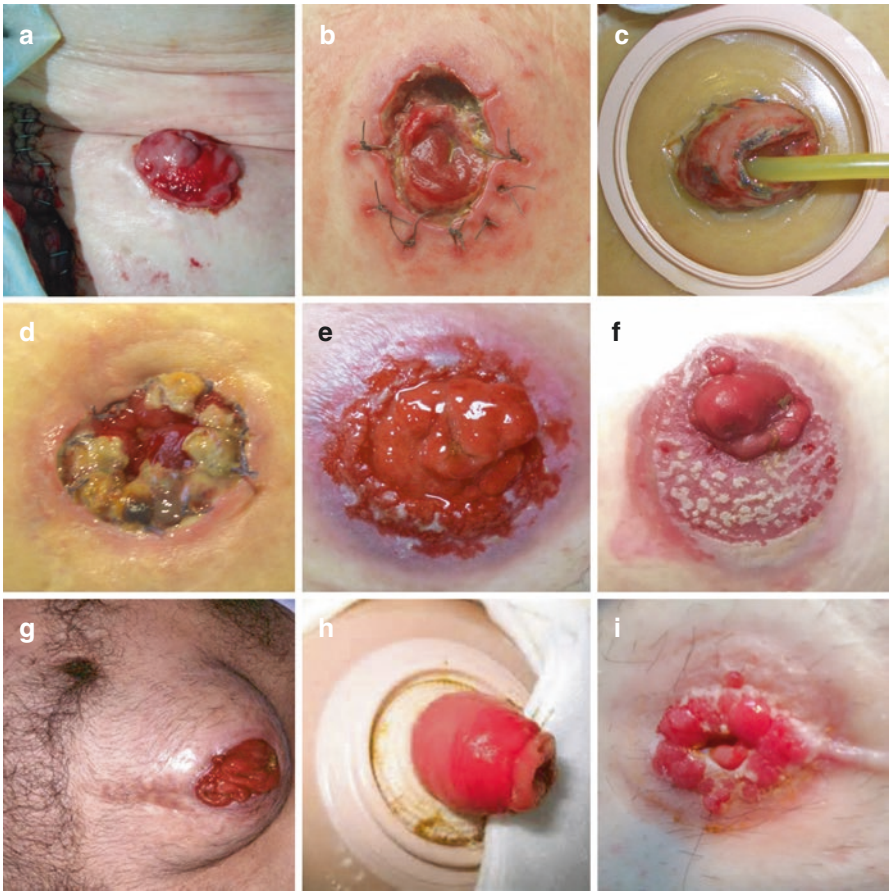

Fig. 3.1 Ostomy complications: (**a**) Improper stoma site selection. (**b**) Colostomy retraction. (**c**) Edema in ileostomy wall with Foley inside the lumen. (**d**) Colostomy wall partial necrosis. (**e**) Ileostomy and skin irritation. (**f**) Skin mycosis surrounding an ileostomy. (**g**) Parastomal hernia. (**h**) Ileostomy prolapse. (**i**) Stoma stenosis

hernias could lead to patient's discomfort, bowel obstruction, and poor appliance fitting. Thus, patients' HRQOL could be critically affected. Symptomatic hernia is an indication of surgical treatment (Fig. 3.1g).

– *Stoma prolapse* (3% of ileostomies, 2% of colostomies) can lead also to pain, poor appliance fitting, obstruction, and incarceration. The highest incidence has been reported for the loop transverse colostomy [42] (Fig. 3.1h).
– *Stoma stenosis* (2–15%) earliest symptom could be a noisy stoma when flatus passing [39] (Fig. 3.1i).

3.3.3.3 Quality of Life in Ostomy Patients

Patients undergoing a stoma placement refer lower overall quality of life, body image, and poorer social activity when compared with CRC patients who had no stoma. Changes in lifestyle, dietary restrictions, and social isolation are frequent within them. Eighteen percent to 26% of the patients with colostomies experience

negative psychological symptoms within the first 3 months of surgery; and these symptoms are commonly anxiety and depression [43]. Moreover, also ostomy caregivers present a relatively higher depression and anxiety than other caregivers [44].

There have been described different instruments for measuring the HRQOL at ostomy patients. The City of Hope Quality of Life Ostomy Questionnaire (COH-QOL) is the most used. This questionnaire was described in 1983 and was further revised and validated for stoma patients [45]. Improved preoperative assessment and counseling with longer follow-up by the stoma specialist would be helpful in the management of these patients. However, the most effective method of preventing a stoma complication remains to be avoiding their formation.

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