Oncologic outcomes following laparoscopic colon cancer resection for T4 lesions: a case–control analysis of 7-years' experience

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Abstract

Background According to many Societies' guidelines, patients presenting with clinical T4 colorectal cancer should conventionally be approached by a laparotomy. Results of emerging series are questioning this attitude.

Methods We retrospectively analysed the oncologic outcomes of 147 patients operated on between June 2008 and September 2015 for histologically proven pT4 colon cancers. All patients were treated with curative intent, either by a laparoscopic or open "en bloc" resection.

Results Median operative time, blood loss and hospital length of stay were significantly reduced in the laparoscopic group. Postoperative surgical complication rate and 30-day mortality did not significantly differ between the two groups ($p = 0.09$ and $p = 0.99$, respectively). R1 resection rate and lymph nodes harvest, as well, did not remarkably differ when comparing the two groups. In the laparoscopic group, conversion rate was 19%. Long-term outcomes were not affected in patients who had undergone conversion. Five-year overall survival and disease-free survival did not significantly differ between the two groups (44.6% and 40.3% vs. 39.4% and 38.9%). Locally advanced stages (IIIB–IIIC) and R1 resections were detected as independent prognostic factors for overall survival.

Conclusion Laparoscopic approach might be safe and acceptable for locally advanced colon cancer and does not jeopardize the oncologic results. Conversion to open surgery should be a part of a strategy as it does not seem to adversely affect perioperative and long-term outcomes. We consider laparoscopy, in expert hands, the last diagnostic tool and the first therapeutic approach for well-selected locally advanced colon cancers. Larger prospective studies are needed to widely assess this issue.

Keywords T4 colon cancer · Locally advanced colon cancers · Infiltrating colon cancers · Laparoscopy · Oncological results · Multi-visceral resection

Colorectal cancer (CRC) accounts for 13% of all cancers, it represents the third most common neoplasia and it stands for the second leading cause of cancer death in the 27 countries of the European Union [1].

Jacobs et al. first reported the technical feasibility of the laparoscopic colectomy in 1991 [2]; since then, many randomized controlled trials and meta-analyses showed laparoscopic colon resections for cancer (LCRC) being safe and, at least, equivalent on long-term outcomes to the open technique.

In experienced hands, LCRC may provide rates of R0 complete resection, lymph nodes retrieval and oncologic outcomes comparable to open procedures [3–7]. In addition to the notable perioperative advantages provided by laparoscopy [8–10], a recent analysis suggested that LCRC could provide even better long-term outcomes in "high-risk" patients (≥80 years, American Society of Anaesthesiologists ≥3, preoperative radiotherapy, T4 tumours and BMI ≥30) compared to open resections [11].

Nowadays however, according to Societies' guidelines, patients affected by clinically staged T4 CRC should be managed by an open approach [12, 13].

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For several years, the laparoscopic multi-visceral dissection has been considered technically demanding, burdensome, lengthy and prone to excessively high conversion rates. Moreover, some authors pointed out the correlation between surgical conversion and increased rates of postoperative morbidity and mortality [9]. Consequently, serious concerns rapidly raised about safety, technical feasibility and oncologic results of the mini-invasive access [14].

Conversely, emerging series are strongly questioning this attitude. Technical skills' development, recent instrumental advancements as well as appropriated patient selection contributed to the extension of laparoscopic working area.

Materials and methods

T4 colon cancer population study

We retrospectively collected 147 patients affected by pT4N0-2M0 colon cancer, electively treated with curative intent between June 2008 and September 2015 (Fig. 1). Among them, 68 patients underwent laparoscopic surgical resection and 79 patients were approached by conventional laparotomy. According to the departmental directives, the choice of surgical access was preoperative set mainly on primary tumour location and on pattern of the nearby organs' infiltration. Previous major abdominal surgery and severe medical conditions were minor reasons for direct open approach.

Preoperative work-up consisted in complete biochemistry, tumour markers, colonoscopy and thoraco-abdominal computer tomography (CT). Virtual CT colonoscopy was performed in case of incomplete preoperative colonoscopy.

The following aspects were investigated: operative time, blood loss, intra-operative complications, postoperative outcomes (hospital length of stay, postoperative complications, perioperative blood loss, 30-day mortality rate, time-frame before adjuvant chemotherapy), completeness of the resection (R0–2), lymph nodes harvest, follow-up period and survival (disease-free survival, overall survival, recurrence rate).

Operative technique

In our surgical department, both conventional surgery and standardized LCRC (right colectomies, segmental splenic flexure resections and left colectomies) are commonly performed since the 1990s.

None of the patients underwent PEG intestinal preparation. All patients were referred to low-fibre diet for 7 days before surgery. Patients with left side colon cancers were subjected to liquid diet and two low-pressure enemas the day before surgery.

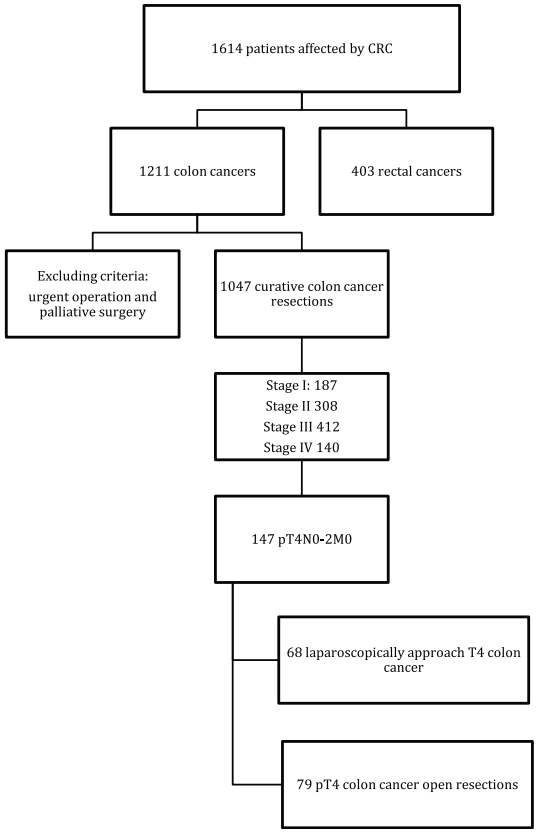

Fig. 1 Flow chart showing patient selection

All 147 patients underwent an "en bloc" surgical resection, extended to tissues involved by the neoplasia. Gentle dissection was conducted according to the rules of the no-touch technique. A wall protector device was always positioned. Surgical procedures routinely included the proximal ligation of blood vessels and the removal of lymphatic bearing segment.

Cancers located along the very distal transverse colon and at the splenic flexure underwent segmental resection with proximal ligation of the left colic and the left branch of the middle colic arteries.

Conversion was defined as a laparotomy performed during the laparoscopic operation, in order to ensure complete resection, reconstruction or haemostasis and not just for the specimen extraction.

Except for the first six laparoscopic right colectomies, an intra-corporeal anastomosis construction was performed for right-sided colon cancers. Closure of the enterotomies was ensured using a double-layer slow-absorbable running sutures.

Postoperative protocols included epidural analgesia for 2 days, liquid fluid diet and gum chewing on first postoperative day, and semisolid diet on second postoperative

day. No naso-gastric tube was left in place. Urinary bladder catheter was removed on the first postoperative day, except in patients who had undergone bladder resection. The intra-abdominal drain, when left in place, was removed on second postoperative day.

Histopathological examination

Histopathological examination included assessment of wall depth of invasion (*T* stage), *N* stage, distal margin status and number of lymph nodes harvest.

Resections were generally defined as R0 resection (negative microscopic margins), R1 resection (positive microscopic margins without gross residual disease) and R2 resection (incomplete resection with gross residual disease).

Follow-up

All patients were postoperatively referred to the Oncologist for adjuvant chemotherapy.

According to European guidelines, patients were subjected to 5-year surveillance program consisting in physical examination and tumour markers (CEA and CA 19.9) dosage every 3 months for the first year and then every 6 months. Complete colonoscopies were recommended at one and three years after the operation. Thoracic and abdominal CT scan were planned every 6 months for 3 years and once a year for the following 2 years of surveillance.

Statistical analysis

Quantitative data are reported as mean, median, standard deviation (SD) and interquartile range (25°–75°%). Qualitative variables are expressed as absolute frequencies and percentages. Differences in categorical data were compared using χ^2 (or Fisher's exact test when appropriated); differences in continuous variables were compared using Student t test or Mann–Whitney test. Univariate analyses of overall survival (OS) and disease-free survival (DFS) rates were performed using the Kaplan–Meyer method. Differences when comparing survival curves were analysed using the Log-Rank test (Mantel Cox). Cox regression analysis was performed in order to identify possible prognostic factors with adjustment for confounders. Results are reported as Hazard Ratio (HR) [95% confidence interval (C.I.)]. A level of 5% was set as the criterion for statistical significance. Statistical analyses were carried out using software R (the R Foundation for Statistical Computing; Version 3.0.3).

Results

Over a 7-year period, 147 patients affected by pT4N0-2M0 colon cancers underwent curative multi-visceral resection in our General Surgery Department in Naples. Among them, 68 were LCRC, while 79 were approached by a laparotomy.

Groups were comparable as far as age, gender, BMI, ASA score, tumour localization and previous surgery were concerned (Table 1).

Sundry organs and tissues resulted infiltrated by T4 colon cancers: small bowel, abdominal wall, duodenal-pancreatic block, Gerota fascia and the retroperitoneum (see Table 2).

Median operative time was 150 min. Laparoscopic operations resulted to be slightly faster than open ones (see Table 3). Median blood loss was 270 ml. Blood loss and hospital length of stay were significantly reduced in the laparoscopic group.

Conversion to open surgery concerned 13 patients (19%): nine patients underwent conversion to safely achieve complete resection, three patients for organ reconstruction (one ureter re-implant and two duodenal resections) and in one case conversion was required to control an uneasy splenic bleeding.

Postoperative surgical complication rate did not significantly differ between the two groups ($p = 0.09$), but were less frequent in the laparoscopic group. Surgical site infections occurred in 11 patients (7.5%). Digestive bleeding occurred in four patients (2.7%): two of them required blood transfusions and there was no need for re-operation. Clinical signs of anastomotic leak occurred in three patients (2%), who underwent re-operation.

No significant differences in postoperative morbidity were detected when comparing patients who had undergone converted and totally laparoscopic colonic resections ($p = 0.99$).

The 30-day mortality rate was 2%. No differences in mortality rate were detected when comparing the two groups ($p = 0.99$). In the laparoscopic group, one patient died for septic complications. In the open one, two patients died for a fulminant myocardial infarction and for a massive pulmonary embolism.

Complete R0 resection was achieved in 88% of the cases in both groups. In the laparoscopic group, the subgroup of converted patients presented an R0 resection rate of 85%, while the totally laparoscopic one of 89%. Median number of lymph nodes harvest in the specimen was 17.4 (±3.9) and 16.3 (±3.7), respectively, for the open and the laparoscopic group. The number of lymph node yield higher than 12 was achieved in all open resections and in 96% of laparoscopic resections. Other oncological features are shown in Table 4.

Table 1 Patients' features

	Laparoscopic ($N = 68$)	Open ($N = 79$)	*p value*
Age			0.57
Mean ± SD	67 ± 11	66 ± 9	
Median [25°–75°%]	68 [59–74]	65 [59–72]	
Sex			0.81
Male	40 (58.8%)	48 (60.8%)	
Female	28 (41.2%)	31 (39.2%)	
BMI			0.95
Mean ± SD	27 ± 3	27 ± 3	
Median [25°–75°%]	27 [25–28]	27 [25–28]	
ASA score			0.72
I	4 (5.9%)	7 (8.9%)	
II	50 (73.5%)	54 (68.4%)	
III	14 (20.6%)	18 (22.75)	
Tumour location site			0.99
Right colon	18 (26.5%)	21 (26.6%)	
Distal transverse colon	7 (10.3%)	8 (10.1%)	
Left colon	43 (63.2%)	50 (63.3%)	
Previous surgery	7 (10.1%)	15 (18.9%)	0.14

Table 2 Organs involved by the T4 colonic tumours

	Laparoscopic group	Open group
Small bowel (except duodenum)	26	32
Abdominal wall	23	24
Duodenal-pancreatic block and pancreatic tail	2	9
Gerota and retroperitoneum	4	9
Bladder	7	3
Gynecologic organs	6	1
Liver/gallbladder/stomach	5	3

Table 3 Perioperative outcomes in laparoscopic and open groups

	Laparoscopic ($N = 68$)	Open ($N = 79$)	*p value*
Type of surgery			0.99
(Extended) right colectomy	18 (26.5%)	21 (26.6%)	
Segmental splenic flexure resection	7 (10.3%)	8 (10.1%)	
Left colectomy	43 (63.2%)	50 (63.3%)	
Operative time (min)			
Median [25°–75°%]	140 [125–160]	160 [140–170]	0.001*
Blood loss (ml)			
Median [25°–75°%]	200 [170–250]	350 [280–450]	$p < 0.001$*
Length of hospital stay (days)			
Median [25°–75°%]	8 [7–9]	9 [9–11]	$p < 0.001$*
Postoperatory morbidity	5 (7.4%)	13(16.5%)	0.09
Clavien-dindo classification			0.99
II	4 (80.0%)	9 (69.2%)	
III	1 (20.0%)	4 (30.8%)	
Mortality within 30 days	1 (1.5%)	2 (2.5%)	0.99

Table 4 Pathologic features and oncologic outcomes in laparoscopic and open groups

	Laparoscopic ($N = 68$)	Open ($N = 79$)	*p value*
pTNM stage			0.90
IIB	33 (48.5%)	36 (45.6%)	
IIIB	27 (39.7%)	32 (40.5%)	
IIIC	8 (11.8%)	11 (13.9%)	
Margin status			0.87
R0	60 (88.2%)	69 (88.5%)	
R1	8 (11.8%)	10 (11.5%)	
Lymph node harvest			0.07
Median [25°–75°%]	15 [14–18]	17 [15–20]	
Adjuvant therapy			0.85
Yes	53 (77.9%)	60 (75.9%)	
No	15 (22.1%)	19 (24.1%)	
Status of patient at the end of follow-up			0.91
Alive	36 (52.9%)	40 (50.6%)	
Died	32 (47.1%)	39 (49.4%)	
Recurrences at the end of follow-up			0.87
No	32 (47.1%)	35 (44.3%)	
Yes	36 (52.9%)	44 (55.7%)	
Follow-up (months)			0.62
Median [25°–75°%]	37 [24–55]	34 [25–46]	

None of the patients received preoperative chemotherapy, while more than 75% of them benefited from adjuvant chemotherapy (mainly XELOX or FOLFOX regimes). No difference in rate of patients who had undergone adjuvant treatment was detected when comparing the two groups ($p = 0.85$).

Median time-frame between surgery and chemotherapy was 36 days (min 28, max 47 days), slightly prolonged in the open group.

Five-year overall survival was 44.6% in the laparoscopic group [CI 32.8–60.6%] and 39.4% in the open group [CI 28.3–55.0%], with no statistical difference detected (see Fig. 2).

Five-year disease-free survival did not differ between the two groups (40.3% in the laparoscopic group, [CI 29.2–55.8%] vs. 38.9% of the open group, [CI 28.8–52.5%], $p = 0.99$) (see Fig. 3).

In the laparoscopic group, no significant differences in both 5-year overall survival (45.8%, [CI 33.3–62.9%] vs. 46.2%, [CI 22.1–84.0%], $p = 0.79$) and 5-year disease-free survival (40.2%, [CI 28.8–57.7%] vs. 43.1%, [CI 23.6–90.4%], $p = 0.86$) were detected between patients who underwent converted colectomies versus totally laparoscopic ones.

Advanced cancer stage (IIIB–IIIC) and R1 margins were independent factors associated with poorer overall survival.

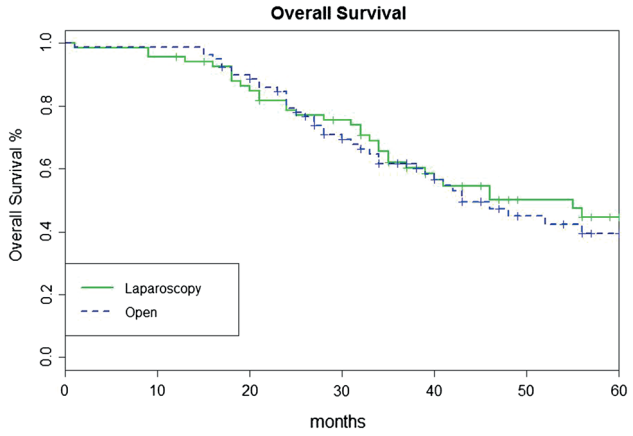

Fig. 2 Overall survival in the compared groups

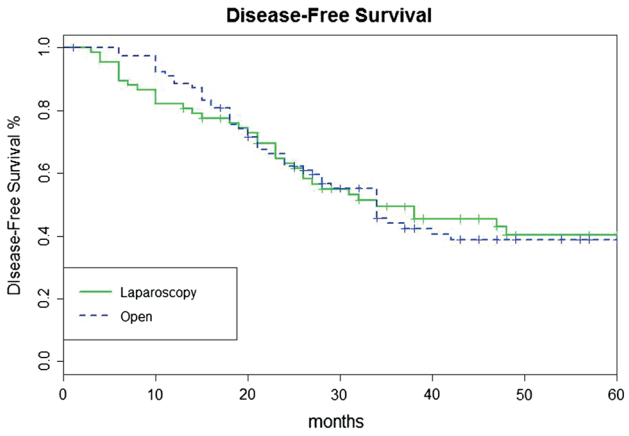

Fig. 3 Disease-free survival in the compared groups

Table 5 Cox multivariate regression analysis to identify possible predictors of mortality in T4 patients (number of deaths: 71)

Variable	Hazard ratio	*p value*
Gender		0.60
Male	1.00 (reference)	
Female	1.14 [0.69–1.89]	
Age		0.40
<65	1.00 (reference)	
≥65	1.25 [0.75–2.09]	
Surgery		0.50
Open	1.00 (reference)	
Laparoscopy	1.18 [0.73–1.92]	
Stage		
IIB	1.00 (reference)	
IIIB	3.47 [1.88–6.43]	$p < 0.001$**
IIIc	24.88 [10.88–56.85]	$p < 0.001$**
Margin status		0.04*
R0	1.00 (reference)	
R1	2.05 [1–04–4.08]	

Table 6 Cox multivariate regression analysis to identify possible predictors of recurrences in T4 patients (number of recurrences: 80)

Variable	Hazard ratio	*p value*
Gender		0.16
Female	1.00 (reference)	
Male	1.40 [0.87–2.24]	
Age		0.66
<65	1.00 (reference)	
≥65	0.90 [0.57–1.43]	
Surgery		0.08
Open	1.00 (reference)	
Laparoscopy	1.51 [0.94–2.40]	
Stage		
IIB	1.00 (reference)	
IIIB	3.60 [2.07–6.27]	$p < 0.001$**
IIIc	27.69 [12.32–62.23]	$p < 0.001$**
Margin status		0.12
R0	1.00 (reference)	
R1	1.70 [0.87–3.29]	

Advanced cancer stage was as well independent prognostic factor for impaired disease-free survival in our analysis (see Tables 5, 6).

Discussion

The surgical treatment of colorectal malignancy has profoundly been changed, in recent years, by the advent of laparoscopy.

Multicentre randomized trials provided extensive evidence of safety and feasibility of colonic resection performed through a mini-invasive access. Moreover, LCRC implied notable advantages in terms of perioperative outcomes when compared to open surgery [8–10]. Recent series have even shown improved long-term outcomes in patients who had undergone LCRC rather than conventional ones, in high volume centres [7]. An improvement in survival was mainly noticed in patients affected by colon cancer staged III according to AJCC (American Join Committee on Cancer) classification [11]. Among reasons advocated to justify better survival, the less compromised immunological response of patients undergoing laparoscopic resections was ascribed [15, 16].

International guidelines have long been recommending to approach locally advanced colonic cancer, a priori, by a laparotomy [12, 13]. International recommendations, however, do not take into consideration important technical evolution and instrumental advancements, which led to very encouraging oncological results [15–19].

At the beginning, in fact, concerns were raised about technical feasibility of the laparoscopic multi-visceral dissection, safe control of intra-operative complications as haemorrhages and operative time prolongation. Moreover, a higher rate of conversion to open surgery was expected, leading to morbidity, mortality and impairment of the oncologic outcome.

As a matter of facts, in CLASICC trial [9], a significant increase in morbidity (69% vs. 47%) and mortality (9% vs. 1%) were recorded in patients who had undergone conversion to open surgery. Some other authors reported adversely affected short- and long-term outcomes in patients who had undergone surgical conversion [9, 20]. Conversely, several series reported no difference in morbidity and/or in mortality whether or not conversion happened in patients affected by colon cancer [21–24].

Conversions reported in the literature ranged from 7.9 to 49% [14, 16, 19, 25].

In our series, conversion rate concerned 13 patients (19%). Among them, all but one was unattended for bleeding, while in 12 patients, conversion was undertaken as a result of an intra-operative decision.

We consider it indispensable to make the difference between an unplanned conversion, needed, for example, to obtain haemostasis in a sudden uncontrollable bleeding or in cases of tumour infringement, and a conversion planned on surgeon's intra-operative evaluation in order to provide a complete resection or reconstruction. In this context, as emphasized by the guidelines [13], the high expertise of the surgeon in LCRC disease is essential to approach locally advanced disease.

In our analysis, perioperative outcomes in the subgroup of patients who had undergone conversion were

comparable to those of the open group. Furthermore, long-term survival in converted group resulted not impaired.

Some short-term outcomes resulted significantly improved in the laparoscopic group.

Less operative time was recorded in the mini-invasive group. This result, discordant to current literature, might be due to the high level of laparoscopic expertise achieved in the department since the 1990s, partially to the 3-dimensional high-definition technology available since 2013 and more likely to the selection bias. Patients with more challenging dissection (as tumour invasion of the duodenal-pancreatic block and the retroperitoneum) were preferably approached by laparotomy.

In the laparoscopic group, less intra-operative blood loss was recorded ($p = 0.001$). Blood loss has been demonstrated to have a predictive role of long-term survival [26, 27].

Hospital length of stay was significantly reduced in the laparoscopic group, confirming that mini-invasiveness permits faster recovery [8–10].

Morbidity and mortality rates were comparable between the two groups, but less frequent in the laparoscopic one.

A proper resection margin (R0) is known to be the most important prognostic factor of long-term survival [28, 29]. Cox multivariate analyses in our series detected marginal status (R) and advanced AJCC stage as independent predictors of long-term mortality.

In the literature, a wide range of R1 open resections for T4 lesions is reported, reaching up to 50%. Data on laparoscopic resections are scarce: in COLOR trial, R1 resections among patients affected by T4 colorectal cancers reached 20%, while Bretagnol et al. reported 13% [9, 25].

Complete R0 resection was achieved in 88% of the cases in both groups. R0 resection rate was 89% in the subgroup of totally LCRC and 85% in the subgroup of converted patients. This difference, testifying the difficulty of dissection of the converted cases and the conversion strategy adopted [30], did not translate into worst short- and long-term results.

Histopathological examination of the specimen confirmed an adequate median number of lymph node retrieval in the both groups.

No negative impact on oncologic outcome was detected in the presence of a small, not significant, difference in lymph node harvest detected between the two groups ($p = 0.07$). All patients approached conventionally had lymph node yield greater than 12, while this occurred in all but three patients in the laparoscopic group, whose yield was 10 for one and 11 for two of them.

Finally, no differences in 5-year overall survival ($p = 0.99$) and in 5-year disease-free survival ($p = 0.79$) were observed when comparing the two groups, suggesting that laparoscopy might be a valid and effective tool to approach locally advanced colon cancer without jeopardize oncologic results, in accordance with previous series reported [15–17, 19, 25–28, 31].

Limits of this study are inhered to the single-centre retrospective design and to patient's selection bias. This approach, however, allowed us to safely provide an extention of the laparoscopic resection's indication for locally advanced colon cancers.

Conclusion

Laparoscopic approach might be safe and acceptable for locally advanced colon cancer and does not jeopardize the oncologic results in well-selected patients. Conversion to open surgery should be a part of a strategy as it does not seem to adversely affect perioperative and long-term outcomes. We consider laparoscopy, in expert hands, the last diagnostic tool and the first therapeutic approach for well-selected locally advanced colon cancers. Larger prospective studies are needed to widely assess this issue.

Compliance with ethical standards

Disclosure Drs. Piera Leon, Michele Giuseppe Iovino, Fabiola Giudici, Antonio Sciuto, Nicolò de Manzini, Diego Cuccurullo and Francesco Corcione have no conflicts of interest or financial ties to disclose.

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