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Aspirin as a neoadjuvant agent during preoperative chemoradiation for rectal cancer

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Background: Recently, many studies have suggested a possible adjuvant role of aspirin in colorectal cancer, reporting a positive prognostic effect with its use in patients with established disease. The aim of this study was to investigate the anticancer effect of aspirin use during preoperative chemoradiation for rectal cancer.

Methods: Two hundred and forty-one patients with stage II–III rectal cancer and candidates for chemoradiation (CRT) were selected and assigned to two groups: group 1, patients taking aspirin at the time of diagnosis, and group 2, all others. Treatment and oncological outcomes were explored.

Results: Aspirin use was associated with a higher rate of tumour downstaging (67.6% *vs* 43.6%, $P=0.01$), good pathological response (46% *vs* 19%; $P<0.001$), and a slightly, although not significant, higher rate of complete pathological response (22% *vs* 13%; $P=0.196$). Aspirin use was also associated with a better 5-year progression-free survival (86.6% *vs* 67.1%; hazard rate (HR) = 0.20; 95% CI = 0.07–0.60) and overall survival (90.6% *vs* 73.2%; HR = 0.21; 95% CI = 0.05–0.89). Although chance of local relapse was similar (HR = 0.6; 95% CI = 0.06–4.5), aspirin use was associated with a lower risk of developing metastasis (HR = 0.30; 95% CI = 0.10–0.86).

Conclusions: Aspirin might have anticancer activity against rectal cancer during preoperative CRT. This finding could be clinically relevant and should be further investigated with randomised trials.

Preoperative chemoradition (CRT) has been demonstrated to improve the rate of local recurrence in locally advanced rectal cancers and it is now standard of care for these patients (Bosset *et al*, 2004; Bujko *et al*, 2006; Gerard *et al*, 2006).

Although CRT could be considered highly effective in this setting, great differences in treatment response still exist among patients receiving such a treatment approach.

In fact, tumour downstaging can be obtained in approximately half of cases and a complete pathological response is reported to range between 15 and 30% (Restivo *et al*, 2013).

Pathological response after CRT has been linked with an improved clinical outcome (Zorcolo *et al*, 2012). As a consequence, several neoadjuvant trials have been designed and conducted with the aim to enhance response rate, particularly pathological complete response. Unfortunately, the addition of new promising chemotherapeutic drugs and molecular targeted agents to classic regimen with 5-FU and radiotherapy has not been as successful as initially planned (Gerard *et al*, 2010; Weiss *et al*, 2010; Aschele *et al*, 2011). Therefore, the search for new and improved treatment options is still ongoing.

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During the past two decades, a convincing body of evidence from large observational studies as well as randomised clinical trials have reported an inverse link between regular use of aspirin and the risk of developing colorectal adenomas and cancers (Baron *et al*, 2003; Sandler *et al*, 2003; Dubé *et al*, 2007; Flossmann *et al*, 2007; Logan *et al*, 2008; Din *et al*, 2010; Algra and Rothwell, 2012). More recently, many studies have reported a positive prognostic effect with aspirin use in patients with established colorectal cancer (Chan *et al*, 2009; Bastiaannet *et al*, 2012; Liao *et al*, 2012; Walker *et al*, 2012; Domingo *et al*, 2013; Ng *et al*, 2015), thus opening the way to investigate its potential role as an adjuvant therapeutic agent.

Although the underlined mechanism is not well understood yet, these results suggest that aspirin could be effective as a single agent and in synergy with the anticancer activity of 5-FU.

This consideration led us to investigate its effect in patients submitted to preoperative CRT for rectal cancer.

MATERIALS AND METHODS

From January 2008 to 2014, all consecutive patients diagnosed with histologically confirmed stage II and III rectal tumour at the Colorectal Surgery Center of the University of Cagliari (Italy) who were candidates for preoperative CRT were enrolled in an observational study investigating the role of chronic aspirin use on clinical outcome. Chemoradiation was routinely proposed to every patient with rectal cancer up to 12 cm from anal verge in pretreatment stage II or III disease.

Patients were assigned to two groups: group 1, including patients who were on aspirin at the start of preoperative CRT, and group 2, including all remaining patients.

Inclusion criteria were as follows:

- histologically proven rectal cancers up to 12 cm from anal verge and
- pretreatment stage II–III.

Exclusion criteria were as follows:

- not giving or not able to give informed consent,
- pretreatment stage I or IV,
- synchronous colon adenocarcinoma,
- concomitant familial polyposis,
- concomitant inflammatory bowel disease (IBD) and
- other contraindications to preoperative chemotherapy and/or radiotherapy.

All patients signed informed consent to participate in the study. The local Ethical Review Board approved this study.

Tumour downstage was assessed comparing clinical preoperative stage to final pathological stage and was graded as follows:

Downstaged: Any lower T or N stage.

Good pathological response (GPR): Downstaged to pT0–T1 N0 tumours.

Complete pathological response (CPR): Absence of any tumour cells.

Main end point of the study was GPR after treatment. Secondary aims were median progression-free survival (PFS) and overall survival (OS).

Patient's clinical and therapeutic data were collected in a dedicated electronic database. One of the physician conducting the study visited every patient and checked for related data integrity during different established occasions as follows: at the time of diagnosis; after initial workup and before initiating CRT; right after the end of CRT; before surgery; after surgery at the time of hospital discharge and 1 month after; and during every subsequent oncological follow-up visit. In particular, chronic use of aspirin was specifically explored at every visit by collecting details on dosage, date of start and, if the case, temporary or definitive interruptions of treatment.

Preoperative treatment consisted in a long course chemoradiation regimen with a dose of 45 Gy administered over a 5-week period (25 fractions of 1.8 Gy per day) with a three-field technique, followed by a tumour boost of 9 Gy for a total dose of 54 Gy. Preoperative chemotherapy was based on 5-FU in daily oral preparation (capecitabine 1650 mg m^{-2} per day) taken during the radiation period.

All patients were included in a follow-up (FU) programme consisting of a flexible rectoscopy every 3 months for the first year, and every 6 months in the second and third year; a complete colonoscopy after the first year, and then after 5 years if negative.

Patients were also monitored with abdominal and chest CT scan every 6 months for the first 3 years, then once yearly until the fifth year; pelvic magnetic resonance imaging (MRI) or endorectal ultrasound every 6 months for 3 years; clinical examination and hematic carcinoembryonic antigen (CEA) dosage every 6 months for the first 3 years, then every year until last follow-up.

The preclinical local stage was assessed by ERUS mostly in combination or sometimes alternatively with pelvic MRI. ERUS procedures were executed all by a single surgeon (Restivo *et al*, 2015). In cases in which both were implemented, agreement between ERUS and MRI in identifying the tumour to submit to CRT was very high, ~95%. However, when in doubt, ERUS was taken as the gold standard in our patients.

The distance of the tumour from the anal verge and its circumferential position was determined by rigid rectoscopy.

Statistics. The collected variables were analysed for significant differences between the two groups. Categorical variables were analysed with Fisher's exact test with Mid-p correction or χ^2 test, whereas continuous variables were tested by Wilcoxon–Mann–Whitney test. Continuous values are expressed in median with 25–75 percentile.

Survival probability was assessed by Kaplan–Meier estimate. Cox proportional hazard regression models were used for survival and outcomes analysis, adjusting for sex, age ($>$ or <65), comorbidity (Charlson score $<=2$ *vs* >2), tumour grade and distance from anal verge ($<=5$ cm *vs* >5 cm), preoperative stage (II *vs* III) and surgery (anterior resection/Hartmann *vs* abdominal–perineal resection/proctocolectomy *vs* local excision). The proportional hazards assumption was satisfied by the Schoenfeld residual method.

All survival analysis were censored at 5 years or last follow-up date, whichever came first: PFS was calculated as the time from enrolment in the study to tumour recurrence or death from any cause; disease-free survival was defined as the time from surgical resection to tumour recurrence or death from any cause; OS was calculated as the time from enrolment to death from any cause. Intent-to-treat analysis was performed using available observations on all participants who entered the study.

Sample size and power. Our hypothesis was that aspirin use during preoperative CRT was associated with a higher rate of pathological response. Based on previous data, the minimum GPR rate for the aspirin group to reject drug efficacy was set to 20% (Bosset *et al*, 2005; Gerard *et al*, 2006). The target number of patients under aspirin use was then set to 33 to detect a 20% difference with an α of 0.05 and 80% power (Machin *et al*, 1997).

RESULTS

In the period of study, 328 patients were diagnosed with rectal cancer up to 12 cm from anal verge. Among those, 87 were not

included because: 12 presented with metastases at initial staging; 64 had a pretreatment stage <II; 2 had a concomitant active IBD; 3 had a synchronous colon adenocarcinoma; and 6 presented with local advanced disease, but preoperative chemotherapy was contraindicated for comorbidities.

Two hundred and forty-one patients, 37 in group 1 (aspirin) and 204 in group 2 (controls), were enrolled in the study from January 2008 to November 2014.

Indication to aspirin treatment was cardiovascular disease prevention in all cases. The daily dose was 100 mg for all patients. Median duration of aspirin therapy before surgery was 5 years (3–8).

Baseline characteristics of the two groups are reported in Table 1. As predictable, considering the indication to aspirin use, patients in this group were older (median age: 71 *vs* 64 years; $P<0.001$) and presented with higher comorbidity. The proportion of male patients was slightly higher in the aspirin group (76.5% *vs* 61.9%), although this difference was not statistically significant ($P=0.101$).

The two groups were homogeneous for other clinical characteristics. Specifically, variables that have been reported to be associated with pathological response such as tumour distance from anal verge, grading, CEA levels before treatment and platelet count were all comparable in the two groups.

Neoadjuvant treatment outcomes. There was one case of grade IV toxicity, a pulmonary embolism in the Control group (0.5%). Grade III toxicity was evident in 4 (11%) and 31 (15%) patients in groups 1 and 2, respectively ($P=0.514$). We observed 29 cases of diarrhoea, 4 (11%) in the aspirin group and 23 (11%) in controls, associated or not with grade III proctitis, which was observed in group 2 only (15 cases, 7%). Preoperative chemotherapy had to be suspended because of hepatic complication not related to treatment (HCV acute infection) in one patient from group 2; however, the patient continued the entire course of radiotherapy. In four cases (all in group 2), the entire course had to be suspended because of a myocardial infarction, one intestinal infarction requiring immediate surgery and two cases of severe proctitis with anemia requiring transfusions.

Pathological response and surgical treatment details are reported in Table 2.

Use of aspirin was associated with a higher chance of tumour downstaging. In particular, the main end point of the study, GPR, was significantly higher in the aspirin group (46% *vs* 19%; $P<0.001$).

Patients in the aspirin group also had a slightly, although not statistically significant, higher rate of CPR (22% *vs* 13%; $P=0.196$).

Thirty-three patients (14%) developed distant metastasis during the preoperative period. Very interestingly, rate of metastasis was significantly lower in patients on aspirin (3% *vs* 16%; $P=0.036$).

All patients proceeded to resection of the primary tumour, but in 10 cases (4%) this consisted in a local excision by transanal endoscopic microsurgery (TEM). Decision was always made after assessment of clinical response. Transanal endoscopic microsurgery was proposed as an alternative to surgery in patients with high surgical risk or refusing radical surgery after CRT.

All other cases were submitted to surgical resection with total mesorectal excision (TME): 157 anterior resections (65%), 68 abdominal–perineal resections (28%), 4 Hartmanns (2%) and 2 proctocolectomies (1%). Tumour was always resected *en bloc*, when necessary with part of other organs (e.g. uterus, bladder, bowel tracts). We did not have any case of more extensive surgery as exenteration or sacrectomy.

Recurrences and survival analysis. Median follow-up was 37 (19–57) months. Aspirin was associated with a better PFS (91.1% *vs* 70.4% at 3 years; 86.6% *vs* 67.1% at 5 years; hazard rate (HR) = 0.20; 95% confidence interval (CI) = 0.07–0.60) and OS (97.1% *vs* 87.3% at 3 years; 90.6% *vs* 73.2% at 5 years; HR = 0.21; 95% CI = 0.05–0.89) (Figure 1 and Table 3). This was a likely

Table 1. Baseline characteristics

Variable	All	Group 1 (aspirin)	Group 2 (controls)	*P*-value
	241 (100%)	37 (15.4%)	204 (84.6%)	
Gender				
Men	155 (64.3)	29 (78.4)	126 (61.8)	0.052
Women	86 (35.7)	8 (21.6)	78 (38.2)	
Age (years)	65 (57–72)	71 (66–78)	64 (56–70)	<0.001
ASA score				
1–2	176 (73)	16 (43.2)	160 (78.4)	<0.001
3–4	65 (27)	21 (56.8)	44 (21.6)	
Charlson score				
1–2	190	22 (59.5)	168 (82.4)	0.004
3–4	51	15 (40.5)	36 (17.6)	
uT				
2	16 (6.6)	3 (8.1)	13 (6.4)	0.696
3–4	225 (93.4)	34 (91.9)	191 (93.6)	
uN				
+	106 (44)	13 (35.1)	93 (45.6)	0.239
−	135 (56)	24 (64.9)	111 (54.4)	
Grading				
1–2	195 (80.9)	30 (81.1)	165 (80.9)	0.977
3	46 (19.1)	7 (18.9)	39 (19.1)	
Distance from anal verge (cm)	7 (5–8)	6 (4–8)	7 (5–8)	0.505
Tumour size (cm)	4 (4–5)	4 (4–5)	4 (4–5)	0.736
CEA (ng dl^{-1})	2.4 (1.5–6.1)	2.1 (1.6–3.2)	2.5 (1.5–6.5)	0.205
Platlet count (10^3)	256 (198–314)	224 (191–277)	261 (209–322)	0.297

Abbreviations: ASA = The American Society of Anaesthesiologists; CEA = carcinoembryonic antigen; uN = pre-treatment N stage; uT = pre-treatment T stage.

Table 2. Pathological response

Variable	All	Group 1 (aspirin)	Group 2 (controls)	*P*-value
CPR	34 (14.1)	8 (21.6)	26 (12.7)	0.196
GPR	56 (23.2)	17 (45.9)	39 (19.1)	<0.001
Downstaged	114 (47.3)	25 (67.6)	89 (43.6)	0.011
Pathological stage				0.019
0	40 (16.6)	9 (24.3)	31 (15.2)	
I	65 (27)	16 (43.2)	49 (24.0)	
II	62 (25.7)	6 (16.2)	56 (27.5)	
III	41 (17)	5 (13.5)	36 (17.6)	
IV	33 (13.7)	1 (2.7)	32 (15.7)	
CRM+	5 (2.2)	1 (3.1)	4 (2)	0.529
Lymphovascular microscopic invasion	51 (21.1)	4 (10.8)	47 (23)	0.089
Lymph nodes harvest	10 (6–15)	10 (6–16)	9 (5–15)	0.823
Surgery				
AR/Hartmann	161 (66.8)	21 (56.8)	140 (68.6)	
APR/proctocolectomy	70 (29)	11 (29.7)	59 (28.9)	0.726[a]
TEM	10	5 (13.5)	5 (2.5)	0.017[a]
Interval CRT-surgery (weeks)	10 (8–12)	10 (8–11)	10 (8–12)	0.348

Abbreviations: APR = abdominal perineal resection; AR = anterior resection; CPR = complete pathological response; CRM = circumferential resection margins (considering patients that underwent surgical resection with total mesorectal excision); CRT = chemoradiation; GPR = good pathological response; TEM = transanal endoscopic microsurgery.
[a]Calculated *vs* anterior resection rates.

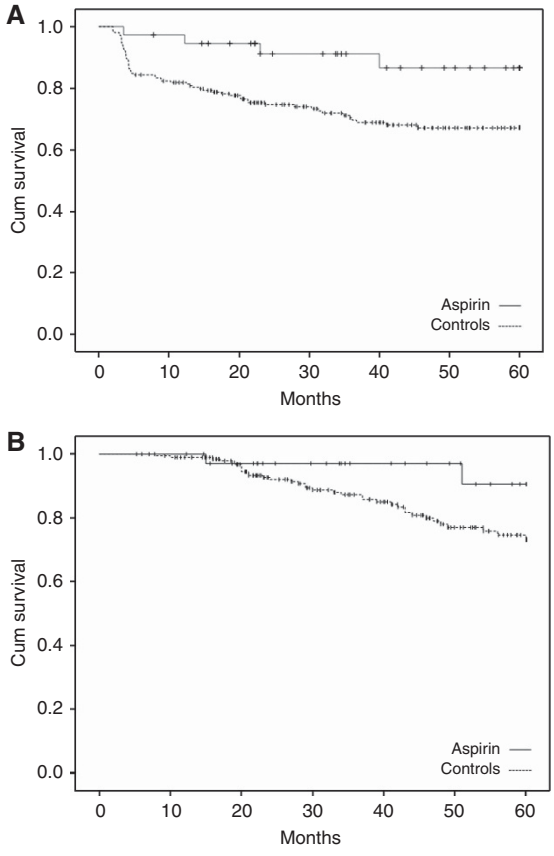

Figure 1. Five year censored Kaplan–Meier curves for: (**A**) progression-free survival (PFS), calculated as the time from enrolment in the study to tumour recurrence or death from any cause; and (**B**) overall survival (OS), calculated as the time from enrolment to death from any cause.

consequence of the lower rate of metastasis in the aspirin group. The overall rate of patients who developed metastatic disease was 23.2% (56 out of 241) in the entire population, 10.8% (4 out of 37) in the aspirin group and 25.5% (52 out of 204) among controls ($P = 0.058$; HR = 0.30; 95% CI = 0.10–0.86).

Nine patients (3.7%) developed local recurrences after surgical resection, 1 (2.7%) patient from the aspirin group and 8 (3.9%) from controls ($P = 0.99$; HR = 0.6; 95% CI = 0.06–4.5).

A subgroup analysis in patients without metastatic disease at the time of surgical resection who underwent a TME with curative intent also showed a slightly better, although not significant, DSF (96.7% *vs* 83.4% at 3 years; 87.1% *vs* 81.2% at 5 years; HR = 0.31; 95% CI = 1.09–1.11) and OS (100% *vs* 93.6% at 3 years; 90.9% *vs* 84.6% at 5 years; HR = 0.20; 95% CI = 0.02–1.67) for patients in the aspirin group.

To explore if the association with survival was independent of CRT response, we performed a *post hoc* analysis adding downstage to the model as an additional covariate. Downstage presented, as predictable, significant better HR for both PFS and OS, 0.27 (95% CI = 00.14–0.52) and 0.25 (95% CI = 0.10–0.59), respectively. Despite that, aspirin was still associated with a significant better HR for PFS (HR = 0.26; 95% CI = 0.09–0.76) and with a better but not significant HR for OS (HR = 0.30; 95% CI = 0.07–1.30).

DISCUSSION

The main finding of this study is that regular aspirin use is associated with a higher rate as well as higher grade of tumour response in patients submitted to neoadjuvant CRT for rectal cancer. The advantage in terms of tumour downstaging seemed clear and clinically relevant. In fact, more than two-thirds of those who were consuming low-dose aspirin during the course of CRT achieved a tumour downstage, leading to cancer regression underneath the submucosae (pT0–T1) in almost 70% of cases.

A positive effect of aspirin against colorectal cancer was suggested for the first time by Kune *et al* (1988), who noticed a significant lower rate of aspirin users among new cases of colon and rectal cancer in Melbourne (Australia) metropolitan area (Kune *et al*, 1988).

Since then, the chemopreventive potential of aspirin has been confirmed by different large cohort studies, in particular through the analysis of data from different large cardiovascular disease prevention trials (Flossmann *et al*, 2007). Recently, Rothwell *et al* (2010), in a pooled analysis, have shown that treatment with any aspirin dose between 75–500 mg per day may reduce risk of colon cancer and associated mortality. Moreover, evidences that its

Table 3. Details of Cox regression analysis for PFS and OS

		PFS		OS	
Covariates	**Reference (1)**	**HR**	**95% CI**	**HR**	**95% CI**
Aspirin	No aspirin	0.2	0.07–0.60	0.21	0.05–0.89
Sex	Male	1.02	0.61–1.72	0.93	0.46–1.89
Age	<65	1.23	0.73–2.09	1.11	0.56–2.25
Charlson score	<3	2.13	1.18–3.81	2.13	1.03–4.37
Pretreatment stage	II	2.09	0.50–8.68	1.99	0.26–14.9
Grading	<3	2.14	1.24–3.72	1.54	0.76–3.12
Distance from anal verge (cm)	<=5	0.78	0.37–1.67	0.68	0.24–1.90
Surgery					
APR	AR	2.05	0.94–4.85	1.88	0.65–5.47
TEM	AR	1.12	0.25–4.97	0.88	0.10–7.46

Abbreviations: APR = abdominal perineal resection; AR = anterior resection; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; TEM = transanal endoscopic microsurgery.

regular use might improve survival on established colorectal cancers are growing, supporting a role of aspirin as an adjuvant agent (Chan *et al*, 2009; Bastiaannet *et al*, 2012; Liao *et al*, 2012; Walker *et al*, 2012; Domingo *et al*, 2013; Ng *et al*, 2015).

Our results suggest that aspirin may also be helpful as a neoadjuvant agent. As this is the first clinical study to report a possible synergic effect with standard preoperative chemoradiation in rectal cancer, no other data are available for direct comparison.

Nevertheless, some *in vitro* studies have already reported positive anticancer interaction of aspirin with both 5-FU-based chemotherapy and radiation. Ashktorab *et al* (2005) showed that aspirin potentiates the apoptotic effect of 5-FU on human colon adenocarcinoma cell line (HT-29). They reported that viability of cells treated with a combination of 1.5 mM aspirin plus 5-FU for 72 h was reduced to 48% compared with 76% of cells treated with 5-FU alone. Kim *et al* (2003), in another interesting study, showed that aspirin may inhibit cell growth of human cervical cancer cells by apoptosis while also acting as a radiosensitive factor (Kim *et al*, 2003). They showed that exposure to 6 Gy radiation in 1 mM aspirin-pretreated cells showed a significant increase of 28.7% in the apoptotic region.

The molecular mechanism by which aspirin could act as an anticancer agent is unclear. The known inhibitory effect of the drug on cyclooxygenase 2 (*COX-2*; prostaglandin-endoperoxide synthase-2) could explain at least part of its effectiveness, as the related pathway has been shown to be overexpressed in >80% of colorectal cancers and in up to 100% of those with metastatic disease (Eberhart *et al*, 1994).

Cyclooxygenase 2 overexpression may enhance tumour growth by various mechanisms, including, among others, stem cell stimulation and promotion of angiogenesis and cancer cell survival by inhibition of apoptosis.

In support of a central role of *COX-2* inhibition, two large cohort studies recently showed that the survival benefit given by regular aspirin use was limited to patients with colorectal cancers in which *COX-2* was overexpressed (Fuchs *et al*, 2005; Chan *et al*, 2009).

Other studies, however, have reported variable results by showing differential independent benefits driven by tumour *BRAF* status and mutations in the gene *PIK3CA*, which may act as components of the *COX-2* pathway(Liao *et al*, 2012; Domingo *et al*, 2013; Nishihara *et al*, 2013), and also by HLA class I antigen expression, which seems independent of the *COX-2* pathway (Reimers *et al*, 2014).

Eventually, aspirin may have more than one target and probably acts in different ways depending on the substrate, dose and duration of therapy. It is well known, for example, that low doses of aspirin (75–300 mg), while producing a partial inhibition of *COX-2* in tissue cells, determine a selective irreversible inhibition of *COX-1* in platelets (Patrignani *et al*, 1982).

In our study, long time use of low-dose aspirin has been related to a significant improvement of PFS and OS. This seemed to be influenced mainly by the overall higher rate of distant relapse in the control group (26% *vs* 11%) and the consequent significant reduced risk of developing metastases in the aspirin group at Cox regression analysis (HR = 0.30; 95% CI = 0.10–0.86). These results are similar to those reported in a recent pooled analysis in which, in colorectal cancer patients without distant disease at initial diagnosis, the HR for later distant relapse was 0.26 (95% CI = 0.11–0.57; $P = 0 \cdot 0008$) (Rothwell *et al*, 2012).

The inhibitory effect of aspirin on platelet activity may explain at least part of its antimetastatic effect. A crucial role of platelets in metastatic progression has been formerly proposed (Gasic *et al*, 1968). Platelets may favor metastatic dissemination by a sort of 'shield' mechanism, protecting circulating tumour cells from immune system attack (Palumbo *et al*, 2005), and support subsequent metastasis growth by favouring angiogenesis (Kisucka *et al*, 2006).

A similar platelet-mediated mechanism could also account for at least part of the effect on tumour response to CRT. Some recent studies, in fact, have reported that thrombocytosis may be a negative predictive factor of response to preoperative chemoradiation in rectal cancer (Kawai *et al*, 2013; Kim *et al*, 2015).

In this setting, aspirin may act by increasing the permeability of tumour vessels, thereby rendering them more susceptible to penetration by foreign agents such as chemotherapeutic drug molecules.

Whatever the molecular mechanism is, our data could suggest that aspirin may have acted during neoadjuvant therapy both locally, enhancing the effect of chemoradiation directed to the primary rectal tumour, and systemically, inhibiting the dissemination and/or growth of metastasis. This last effect is very suggestive and seems to be indirectly confirmed by the survival analysis. Despite presenting with higher comorbidity and older age, in fact, patients in the aspirin group still achieved a significant better PFS and OS, suggesting that the effect on distant metastasis and survival could be even greater in the general population.

The main limitation of the study comes from its observational nature. As there was no active indication for its anticancer activity, patients were all taking aspirin before the diagnosis of cancer was made.

It can be questioned that the observed effects on tumour response and survival could actually be secondary to better biologic behaviour given by long time aspirin use before diagnosis rather than on a synergic effect for established cancer.

Although this possibility cannot be ruled out, it has to be noticed that all the known markers of biologic aggressiveness were comparable between aspirin and controls, making this eventuality unlikely. Another limitation is that, despite different studies having reported an association between various molecular markers and susceptibility to the anticancer effect of aspirin, we did not consider those markers in the multivariate analysis. We decided to include an unselected rectal cancer population, primarily because those gene expression analyses were not part of our routine workup. This limitation, however, could have only led us to underestimate the influence of aspirin in a possible more responsive subgroup.

In summary, this is the first study to propose a role of aspirin as a neoadjuvant therapeutic agent in rectal cancer. Given the observational nature and the relative small sample size, our data should be interpreted cautiously, but we suggest further investigating with a randomised trial the oncological benefit of including aspirin into the CRT regimen.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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