Clin Transl Oncol (2013) 15:443–449
DOI 10.1007/s12094-012-0949-1

RESEARCH ARTICLE

Intraoperative radiotherapy for the treatment of resectable locally advanced gastric adenocarcinoma: topography of locoregional recurrences and long-term outcomes

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Received: 14 August 2012 / Accepted: 20 September 2012 / Published online: 10 November 2012

Abstract
Introduction To report feasibility, tolerance, anatomical sites of upper abdominal locoregional recurrence and long-term outcome of gastric cancer patients treated with surgery and a component of intraoperative electron beam radiotherapy (IORT).
Materials and methods From January 1995 to December 2010, 32 patients with primary gastric adenocarcinoma treated with curative resection (R0) [total gastrectomy ($n = 9$; 28 %), subtotal ($n = 23$; 72 %) and D2 lymphadenectomy in all patients] and apparent disease confined to locoregional area [Stage: II ($n = 15$; 47 %), III ($n = 17$; 53 %)] were treated with a component of IORT (IORT applicator size 5–9 cm in diameter, dose 10–15 Gy, beam energy 6–5 MeV) over the celiac axis and peripancreatic nodal areas. Sixteen (50 %) patients also received adjuvant treatment (external beam radiotherapy $n = 6$, chemoradiation $n = 9$, chemotherapy alone $n = 1$).
Results With a median follow-up time of 40 months (range, 2–60), locoregional recurrence was observed in five (16 %) patients (4 nodal in hepatic hilum and 1 anastomotic). Only pN1 patients developed locoregional relapse. No recurrence was observed in the IORT-treated target volume (celiac trunk and peripancreatic nodes). Overall survival at 5 years was 54.6 % (95 % CI: 48.57–60.58). Postoperative mortality was 6 % ($n = 2$) and postoperative complications 19 % ($n = 6$).
Conclusions It is feasible to integrate IORT as a component of radiotherapy in combined modality therapy of gastric cancer. Local control is high in the radiation boosted area, but marginal regional extension (in particular, involving the hepatic hilum) might be considered as part of the anatomic IORT target volume at risk in pN+ patients.

Keywords Intraoperative radiotherapy · Gastric adenocarcinoma · Locoregional recurrence

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Introduction

A worldwide experience generated in the last 20 years has shown that intraoperative radiation therapy (IORT) is a feasible technique for incorporation in gastric cancer surgery [1]. Surgical resection remains the only curative option for gastric adenocarcinoma; nonetheless, it is curative in less than 40 % of the cases. Locally advanced transmural tumors have an increased risk of nodal metastases with resultant decrease in disease-free survival (DFS) and 5-year overall survival (OS) of 20–30 % [2]. Post-

treatment failures are primarily intra-abdominal, and local failures after surgery of curative intent range between 38 and 85 % [3] reaching 87 % when nodes are positive [4]. Current knowledge on patterns of failure for gastric cancer after postoperative chemoradiation suggests a 19 % local failure rate and 65 % regional recurrence [5].

Total dose of radiotherapy that can be delivered even with the most sophisticated and updated external beam radiotherapy (EBRT) techniques is limited by the presence of dose-limiting surrounding organs or structures in the planned treatment volume (PTV). IORT enables the delivery of relatively large doses of radiation in a single fraction to the upper abdominal nodal regions and tumor bed, with the advantage of displacing dose-limiting tissues (duodenum, transverse colon, liver, small bowel and kidney). An IORT boost component has also been included in the context of neoadjuvant chemotherapy, surgical resection and EBRT with acceptable tolerance and improved local control (3–44 %) [6]. There is indirect evidence from Fu et al. [7] that IORT used in combination with adjuvant concurrent chemoradiotherapy for T3/4 or N+ gastric adenocarcinoma may improve locoregional control rates compared with chemoradiation alone.

This study analyses the outcome on the basis of long-term efficacy and toxicity profile of treatment combination (including an IORT component) in the management of locally advanced gastric cancer, with particular emphasis on the topography of cancer recurrence in the upper abdominal region.

Materials and methods

From January 1995 to December 2010, 32 patients [15 female, 17 men, median age, 59 years (range 31–74 years)] who had pathologically confirmed stage II or III gastric adenocarcinoma (AJCC/UICC staging classification 2010) were treated with multimodal treatment and IORT at the Gregorio Marañon General University Hospital in Madrid, Spain (Table 1). Pretreatment evaluation consisted of a complete history and physical examination, serum chemistry, chest X-ray, esophago-gastro-duodenoscopy and computed tomography (CT) of the abdomen. Positron emission tomography (PET) was available in the later years of the study. Patients who had metastatic disease, apparent T1–T2 disease without enlarged regional lymph nodes and non-curative resection were excluded from this study. Surgery was performed through a median laparotomy or subcostal bilateral incision (Chevron) and surgeons were free to select either total [$n = 9$; (28 %)] or subtotal gastrectomy [$n = 23$; (72 %)] (according to the tumor location) combined with a D2 lymph node dissection for all patients. The same two senior surgeons were in charge of the surgical interventions during the IORT gastric cancer program.

Table 1 Patient, tumor and treatment characteristics

Characteristics	
Median age	60 (range 31–74)
Gender	
Male	17 (53 %)
Female	15 (47 %)
Tumor location	
Cardias	9 (28 %)
Body	14 (44 %)
Antrum/pylorus	9 (28 %)
pT stage[a]	
pT2	6 (18 %)
pT3	16 (50 %)
pT4	10 (32 %)
pN stage[a]	
pN0	16 (50 %)
pN1	16 (50 %)
Overall stage[a]	
II	15 (47 %)
III	17 (53 %)
Residual disease	
R0	32 (100 %)
Surgery technique	
Total gastrectomy	9 (28 %)
Subtotal gastrectomy	23 (72 %)
Adjuvant treatment	16 (50 %)
Radiotherapy	6 (18 %)
Chemoradiation	9 (28 %)
Chemotherapy	1 (3 %)
None	16 (50 %)
IORT	
Median dose	12.5 Gy (range 10–15)
Median cone size	7 cm (range 6–9)
Median beam energy	9 MeV (range 6–15)

IORT Intraoperative radiation therapy

[a] AJCC 7th Edition staging

IORT was delivered using a linear accelerator located next to the surgical theater. At the end of the surgical exeresis and before performing digestive anastomosis, a cylindrical and beveled plastic collimator was inserted into the abdomen (Fig. 1). Irradiation was focused on the tumor bed in case of extensive transmural disease (pathological examination of frozen sections) and on the high-risk lymph node groups along the left gastric, splenic arteries, celiac axis and central upper peripancreatic region. The size of the beam collimation (5–9 cm in diameter) depended on the area to be treated. The fields were shaped with appropriate

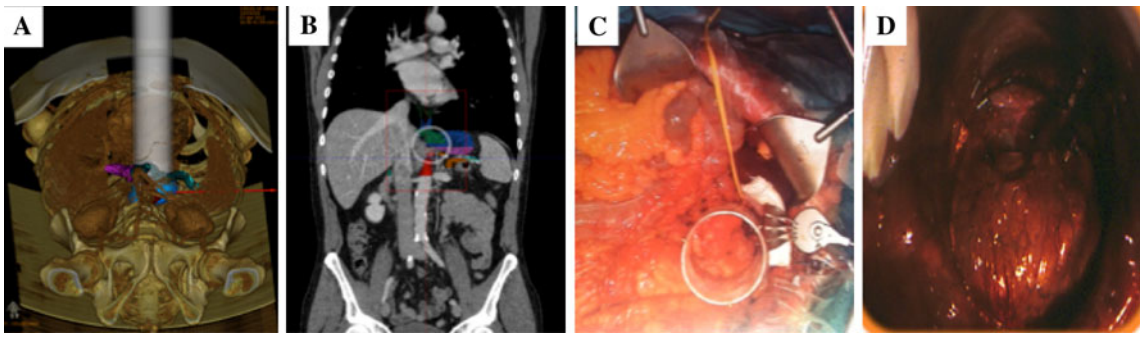

Fig. 1 3D (**a**) and 2D (**b**) CT scan-based reconstruction technology. (**c**) Mobile normal tissues are displaced from the IORT field including duodenal, gastric or esophageal stump, transverse colon, small bowell and kidney. (**d**) Celiac trunk, peripancreatic nodal region and gastric tumor bed area are included in the IORT target volume. Hepatic hilium is partialy included in its lower medial area

shielding blocks to confine the radiation beam to the desired anatomic area. Gauze pads were used to displace/immobilize the surrounding sensitive structures such as small bowel and liver out of the radiation field. This procedure means. regularly. the addition of 30 min to the surgical time. Transportation time did not usually exceed 3 min (each way). The prescribed doses were 1,000 or 1,500 cGy according to the probability of residual disease assessed by the surgeon and prescribed to the 90 % isodose line [8]. The energy of electrons (6–15 MeV) was determined according to the diameter of the collimator cone used and the depth of tissues considered as the target of treatment. Adjuvant treatment was based on tumor board consensus judgment.

EBRT was delivered with a 15-MV photon beams linear accelerator, 4 weeks after surgery. The clinical target volume, defined according to the Report 50 from the International Commission on Radiation Units and Measurements (ICRU), included celiac area as well as the tumor bed or other lymph nodes' area (cardia, suprapyloric, infrapyloric, common hepatic artery, celiac artery, splenic hilus) depending on resection margins and lymph node involvement on the pathologic specimen. A four-field technique (anterior, posterior with 1–2 lateral fields depending on dose coverage and the volume of the kidney) was used. Standard 1.8 Gy daily fractions were used to deliver a median total EBRT dose of 45 Gy, prescribed and specified at the ICRU point (intersection of the central axes of the four beams). The chemoradiation adjuvant regimen was cisplatin and 5FU or 5FU–leucovorin (INT 0116 regimen) [5].

Patients were followed clinically every 3 months after the completion of treatment in the initial 3 years, then every 6 months for 3 additional years thereafter. Follow-up examinations included complete history and physical examination, serum chemistry, ultrasound of liver, CT of the chest and abdomen, as well as endoscopy, which were performed routinely. When signs or symptoms of recurrent disease were present, ultrasonography, abdominal computed tomography and gastroscopy were performed.

Acute and late toxicities from treatment were graded according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria [9]. Late toxicities were defined as symptoms first occurring or lasting >90 days after the completion of radiotherapy. Survival and recurrence data were collected prospectively. All patients were followed up until death or until the date of the last follow-up visit for patients still alive. Overall survival, local control and disease-free survival were estimated using the Kaplan–Meier method. Prognostic factors for survival and recurrence were evaluated using the log-rank test.

Results

The median follow-up for all patients was 40 months (range 2–60 months). The pathologic stage of all tumors was consistent with the preoperative clinical stage. A pathologically confirmed complete resection was achieved in all patients.

The median survival time was 60 months (95 % CI: 53.41–66.59) for the entire group of patients. At analysis, 13 patients (41 %) had disease recurrence and 14 patients (44 %) had died (1 patient died of intercurrent causes). Distant recurrences developed in eight (25 %) patients at their first site of recurrence, four (12.5 %) patients developed both local and distant relapses synchronously and one (3 %) patient developed exclusive locoregional (LR) recurrences. The most common site of LR recurrence was hepatic hilum in four (12.5 %) patients and anastomotic in one (3 %) patient. No recurrence was observed in the IORT treated target (celiac trunk and peripancreatic nodes) (Table 2). Among patients with distant metastases

Table 2 Overall survival, disease-free survival and topographic pattern of metastases

Results	
5-year overall survival	54.6 % (95 % CI: 48.57–60.58)
Overall survival median time	60 months (95 % CI: 53.41–66.59)
Disease-free survival median time	42.4 months (95 % CI: 34.71–50.17)
Synchronous systemic and local relapse	4 (12.5 %)
Systemic relapse alone	8 (25 %)
Local relapse alone	1 (3 %)
Topography of locoregional failure	
Hepatic hilum	4 (12.5 %)
Anastomosis	1 (3 %)
Celiac trunk	0
Tumor bed	0
None	27 (84.5 %)

Table 3 Impact of adjuvant treatment delivered and pT and pN classification on locoregional relapse

	Recurrence (+)	Recurrence (–)	*p*-value
Adjuvant treatment	3 (19 %)	13 (81 %)	0.097
Radiotherapy	0	6 (100 %)	
Chemotherapy	1 (100 %)	0	
Chemoradiotherapy	2 (22 %)	7 (78 %)	
None	2 (13 %)	14 (87 %)	
pTNM classification			
pT2N0	0	5 (100 %)	0.079
pT2N1	1 (100 %)	0	
pT3N0	0	10 (100 %)	
pT3N1	2 (29 %)	5 (71 %)	
pT4N0	0	2 (100 %)	
pT4N1	2 (29 %)	5 (71 %)	

recurrences, the most common sites of progression were liver ($n = 3$) and peritoneum ($n = 7$). Five-year overall survival (OS) was 54.6 % (95 % CI: 48.57–60.58) and the median disease-free survival was 42.4 months (CI: 34.71, –50.17) (Table 2). The locoregional control rate did not differ based on adjuvant treatment delivered ($p = 0.097$) or pTNM classification (0.079) (Table 3). Only pN+ patients developed locoregional relapse. Of the 32 patients, 30 (94 %) completed the entire treatment course without interruption. The most commonly observed severe acute complication (defined as Grade 3 and 4) seen during external beam radiotherapy group ($n = 15$; 47 %) was leukopenia, which developed in six patients. Radiation-induced Grade 3 or greater acute digestive toxic effects, such as nausea/vomiting, weight loss, dyspepsia and diarrhea, were observed in five patients in the IORT + EBRT group. All patients recovered with supportive treatment. In the immediate postoperative period, complications were observed in six (19 %) patients that consisted of five suture dehiscence requiring reoperation and one pancreatic fistula. Two (6 %) patients died in the postoperative period with uncontrolled intra-abdominal complications.

Discussion

Treatment-induced toxicities remain a long-term clinical challenge in the treatment of gastric cancer using chemoradiation [5, 10]. The tolerance of upper abdominal organs and structures to external beam radiotherapy following gastric resection has been tested in several clinical trials reported previously [11–13]. Few events were described as major toxicities potentially induced by radiotherapy, which implies that an acceptable clinical tolerance might be assumed from those trials (adjuvant target volumes and total doses), if the technical aspects involved in delivering the treatment are followed meticulously [14]. Large radiation dose per fraction increases late toxicity; however, reports on late toxicity after IORT are scant [15]. The tolerance of vasculature and stomach after surgery to IOERT with or without EBRT has been investigated in animal and clinical models [16, 17]. The late effects observed in animal experiments suggest that 10–20 Gy IOERT plus EBRT dose of 45–50 Gy do not compromise the outcome of healthy adult animal. The damage to the intrinsic vasculature and connective tissue of organs observed in the examined specimens seems to be responsible for the damage to the organ with an increasing degree of severity depending on IORT dose escalation [18]. In the clinical setting, long-term tissue changes are rarely histologically evaluated, and long-term survivors usually experience multiple treatment protocols. However, animal experiments in IORT radiobiology cannot completely mirror human response. Our long-term cohort follow-up has proven that multimodal treatment with IORT is feasible with low perioperative morbidity [5 suture dehiscence ($n = 2$ total $n = 3$ subtotal gastrectomy) requiring reoperation and 1 pancreatic fistula] and no patient experienced Grade 3 or 4 late complications. Second malignancy is another concern [19]. Undifferentiated or sarcoma-like tumor has been reported within the IORT field after long-term follow-up [20]. The median follow-up of 40 months in the present cohort is clearly too short to address the issue of second malignancy.

Local control by radiation for subclinical disease is a function of radiation dose [21], and extended interval

between surgery and radiation allows accelerating proliferation of cancer cells under stress [22]. Therefore, it is reasonable to postulate that a high single dose delivered early in the course of treatment could further improve disease control of gastric cancer after surgical resection [23]. It remains to be determined whether precise high-dose RT to a similarly planned tumor volume using intensity-modulated RT or proton therapy without IORT can obtain a comparable improvement in outcome [24]. The specific patterns of cancer progression within the anatomical upper abdominal regions following IORT have not been reported previously. In our experience, a total of five patients (15.5 %) developed local relapse as a component of failure in this report. Four out of five (80 %) LR recurrences occured in the hepatic hilum and none within the IORT field, highlighting the need of a specific analysis to evaluate the precise patterns of topographic failure, using patient 3D anatomy reconstruction and virtual planning (IORT and EBRT) [25]. Any intent to compare the present data with previous clinical reports using IORT in gastric cancer patients will have important methodological objections. The tumor staging classification has changed in the last decade, regrouping patients with different pathologic features, and asking for certain information that will probably not be available from past analysis and even in most contemporary studies [26].

Despite significant advances in disease control, the outcome after surgery followed by adjuvant chemoradiotherapy remained suboptimal, with local or regional recurrences at approximately 19 and 65 %, respectively, after the tri-modality therapy [7]. About 25 % of patients had distant metastases in our experience, emphasizing the need for more effective systemic therapies. Despite our favorable results [overall survival at 5 years was 54.6 % (95 % CI: 48.57–60.58)], the use of IORT with more standard adjuvant treatment (i.e., chemotherapy and EBRT) has rarely been prospectively addressed [7]. In addition, most studies included patients with both locally advanced and early-stage gastric cancer. Therefore, it was not surprising that the benefit of the previously studied radiation regimen was limited to locoregional control (Tables 4, 5). Although postoperative 5-FU-based chemotherapy and RT (45 Gy in 25 fractions) has been adopted as the standard adjuvant treatment modality in the USA for locally advanced gastric cancer after definitive gastrectomy, and the role of neoadjuvant plus adjuvant chemotherapy has been clearly addressed in the Medical Research Council

Table 4 Treatment regimens and outcomes in IORT + EBRT trials for gastric cancer

Author, year, institution	N, stage, resection	Radiation dose	EBRT (%)	ChT (%)	LRC, time point	OS, S+ IORT
Dulce (1991) Berlin, Germany	26, resectable	IORT 12-16 Gy; EBRT 24-38 Gy[a]	100	n/a	Not reported	Stage III 67 % 2-year
Calvo (1992) Navarra, Spain	48, AJCC I-IV, recurrent	IORT 15 Gy; EBRT 40-46 Gy[b]	89	27	90 %	5-year, T3,4 33 %; T1,2 56 %
Avizonis (1995), RTOG 85-04, USA	27, AJCC Ib-IV	IORT 12.5-16.5 Gy; EBRT 45 Gy[b]	85	0	63 %	2-year 47 %, MST 19 months
Chabert (1996), CHU Bellevue, France	21, II-IV	IORT 15-20 Gy; EBRT 28-46 Gy	52	n/a	67 %	5-year 32 %, MST 19 months
Coquard (1997), Lyon, France	63, I-IV	IORT 15 Gy; EBRT 44-46 Gy[a]	48	17	5-year 76 %	5-year 47 %
Martinez-Monge (1997) Navarra, Spain	27, S+ and/or N+	IORT 15 Gy; EBRT 40-46 Gy[b]	100[c]	4	89 %	12-year 41 %
Glehen (2000), Paris, France	87, resectable T1-4, N0-2M0	IORT 12.5-16.5 Gy; EBRT 45 Gy	n/a[d]	16	5-year 79 % in N+	5 year R0 60 %; R0-pN0 90 %; R0pN+ 55 %
Skoropad (2000), Obninsk, Russia	78, resectable T1-4, N0-2M0	Phase III study: S vs. EBRT 20 Gy + S/IORT 20 Gy	100	0	Not reported	MST 21 months; 5-year 40 %
Weese (2000), Graduate H, USA	15, AJCC IIIA-IV	CAFL[e] + IORT 20 Gy; EBRT 45 Gy	100	100	2-year 93 %	MST 21 months; 5-year 47 %
Lowy (2001) MDACC, USA	24, AJCC Tx-4	EBRT 45 Gy/F; IORT 10 Gy	100	100	Not reported	Not reported
Glehen (2003), Lyon, France	41, N1, N2	IORT 15 Gy; EBRT 45 Gy	86	16	5-year 79 %	10-year 45 %

Table 4 continued

Author, year, institution	N, stage, resection	Radiation dose	EBRT (%)	ChT (%)	LRC, time point	OS, S+ IORT
Miller (2006), Mayo, USA	50, G&E[f], R0 42%; R1 46%; R2 12%	IORT 10-25 Gy; EBRT 50.4 Gy	96	92	3-year local 90 %; 3-year regional 85 %	MST 21 months[g], 3-year 27 %
FU (2008), Shangai, China	97, AJCC T3,4± N+	Non-randomized comparison: EBRT 45 Gy/DPF[h] vs. IORT 12-15 Gy + EBRT 39.6 Gy/DPF	100	100	3-year 77 %	3-year 56 %, MST 38 months

N patient number, *LRC* local-regional control, *OS* overall survival, *MST* median survival time, *S* surgery, *ChT* chemotherapy, *EBRT* external beam irradiation, *IORT* intraoperative irradiation

[a] Four-field technique

[b] Field as derived from University of Minnesota reoperation data

[c] Only stages B2-C3 who completed the radiation course were included

[d] Only given to patients with T3 and/or N+ tumors

[e] Adriamycin, cisplatin, 5-fluoroucil, and leucovorin neoadjuvant chemotherapy

[f] Locally primary advanced or recurrent gastric and esophageal tumors

[g] Primary 3 years; recurrent 1.3 years ($p < 0.05$)

[h] Docetaxel, cisplatin, 5-fluoroucil, and leucovorin chemoradiation

Table 5 Treatment characteristics and outcomes in IORT-alone trials for resected gastric cancer

Author, year, institution	*N*, stage, resection	Radiation dose	LRC, time point	OS, time point
Abe (1988), Kyoto, Japan	101, JSSS I–IV, gross findings	Phase III study: IORT 28–40 Gy versus none	NR	5-year; stage II 83 %, stage III 62 %, stage IV 15 %
Sindelar (1993), NCI, USA	15, AJCC III–IV	Phase III study: IORT 20 Gy versus EBRT 50 Gy[a]	56 %[b]	MST 25 months; 5-year 10 %
Farthmannn (1993), Freiburg, Germany	36	IORT 25–28 Gy	2-year 97 %	2-year 50 %
Abe (1988), Kyoto, Japan	94, JSSS I–IV, Gross findings	Phase III study: IORT 28–40 Gy versus none	NR	5-year; stage II 78 %, stage III 60 %, stage IV 33 %
Ogata (1995), Kochi, Japan	58, JSSS II–IV	IORT 28–30 Gy	NR	5-year; stage II 100 %, stage III 55 %, stage IV 14 %
Kramling (1997) Munich, Germany	51	IORT 28 Gy	NR	MST 26.9 months
Qin (2006), Shangai, China	106, I–IV	IORT 10–30 Gy[c]	NR	5 year stage I, II 100 %, stage III 60.4 %, stage IV 14.3 %
Drognitz (2008), Freiburg, Germany	61, AJCC I–IV	IORT 23 Gy	5-year 90 %[d]	5-year 58 %

N patient number, *LRC* locoregional control, *OS* overall survival, *NR* not reported, *MST* median survival time

[a] EBRT only given to stage III–IV patients

[b] Nonstandard criteria for definition of locoregional failure. The overall locoregional failure rate of 44 % for the IORT arm and 92 % for the surgery ±EBRT arm ($p < 0.001$)

[c] 10–15 Gy if no clinically undetectable lesions; 20 Gy if microscopic residual nodes were suspected; 25 Gy if macroscopic residual nodes or direct invasion of adjacent structures; 30 Gy to one patient who had non-curative surgery because of incomplete excision of metastatic lesions

[d] Locoregional control data for non-IORT control group

Adjuvant Gastric Infusional Chemotherapy trial [27], it is still relevant to study the efficacy of IORT used in combination with other treatment modalities, especially those that have a proven efficacy, to explore whether additional synergistic therapeutic effects are present. A component of the dose delivered with IORT will allow intensifying radiotherapy with minimal normal tissue toxicity risk.

Conclusion

It is feasible to integrate IORT as a component of radiotherapy in multimodal therapy of locally advanced gastric cancer. Local control is high in the boosted area, but regional extension (in particular, to the hepatic hilum) might be considered part of the anatomic target in pN+ patients. However, the outcome of patients with locally advanced gastric cancer remains suboptimal after such intensive treatment, and the optimal modality of RT delivery is yet to be determined. Escalated radiation doses with concurrent chemotherapy used in the adjuvant setting is a strategy that deserves to be explored and optimized. Prospective multimodal trials considering IORT offers an opportunity to further improve outcomes.

Conflict of interest We do not have any financial relationship that may lead to a conflict of interest in relation to the submitted manuscript.

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