Results of the management of rectal cancer have enormously improved over the last almost forty years, by the progressive development of new integrated treatment options, nevertheless an optimization of the results is needed to raise the still sub-optimal outcome in terms of survival. Several national and international guidelines address the best treatment choice overall evaluating the evidence basis available from literature. Still a certain degree of disagreement is present, particularly about the preferable preoperative RT treatment schedule.

Randomized trials represent the main landmark and most important tool for the scientific scenario: defining a potentially established standard of care, or suggesting the more promising approach to focus the research into, thus orienting the efforts of clinicians and researchers. This manuscript will mainly focus on the evidences derived from randomized clinical trial describing the main issues about the multimodal integrated treatment for rectal cancers. It will focus on both locally advanced (LA)/primary unresectable (UR), and resectable rectal cancers; some non-randomized trials of relevant the dissertation will also be mentioned.

Key words: rectal cancer, combined modality treatment, preoperative radiotherapy, surgery, postoperative radiotherapy, chemotherapy.

INTRODUCTION

Results of the management of rectal cancer have enormously improved over the last almost forty years, by the progressive development of new integrated treatment options.

In particular: the exploit of new surgical techniques (in the surgical area of interest), the evolution of modern radiotherapy, often associated to chemosensibilization, the standardized evaluation of surgical specimens, and the recent advantages of proper non-invasive radiological imaging to better perform both staging and the evaluation of prognostical features overall did contribute to the standard quality-level for the integrated treatment of such tumors. Nevertheless an optimization of the results is needed to raise the still sub-optimal outcome in terms of survival. Several National and International Guidelines address the best treatment choice overall evaluating the evidence basis available from literature. Still a certain degree of disagreement is present, particularly about the preferable preoperative RT treatment schedule.

Randomized trials represent the main landmark and most important tool for the scientific scenario: defining a potentially established standard of care, or suggesting the more promising approach to focus the research into, thus orienting the efforts of clinicians and researchers. On the other hand, new paradigms of approach are currently under definition and evolution, that challenge and simultaneously integrate the use of randomized clinical trials (RCT), as the always wider use of rapid learning machines, and the investigation of surrogated endpoints. Anyway in order to summarize the main evidences on the current knowledge about the treatment of rectal cancers, it is imperative to refer to RCTs, also to address further studies on the more evident and urgent controversies. Aims of this paper is to review the main issues about the multimodal integrated treatment for rectal cancers focusing on both locally advanced (LA)/primary unresectable (UR), and resectable rectal cancers.

MATERIALS AND METHODS

The manuscript will mainly focus on the evidences derived from RCT; some non-randomized trials of relevant the dissertation will also be mentioned.
Issues described will include: the role of radiotherapy (RT) among integrated treatments; the modification of integrated approach replacing the postoperative RT with preoperative RT; the debate on the choice between short course RT (SCRT) and long course radiochemotherapy (LCRTCT); the new challenges for the optimization of the drugs associated into the LCRTCT regimens; the modulation of surgical approach after preoperative RT; the importance of the involvement of circumferential margins (CM).

**Dissertation**

**Locally Advanced and Primary Unresectable Tumors**

What tumor type belongs to the unresectable presentations is a quite clear and objective concept; on the other hand, the locally advanced presentations heterogeneously include both lesions with a tough margin for attempting a resection (eventually defined with the aid of clinical evaluation), and fixed lesions invading structures close to the rectum. Not clearly upfront-resectable presentations also include: the threatening or infiltration of mesorectal fascia (MRF) or the direct involvement of the sphincter (see also below).

In general the common standard of treatment for T4 and/or locally unresectable (including locally recurrent) rectal cancers is represented by LCRTCT with a 5-Fluorouracil (5-Fu)-based regimen. The randomized trial published by Braendengen et al. on patients with unresectable or recurrent lesions addressed this issue. They randomized 98 patients to either RT alone (50Gy) or to concurrent LCRTCT with 5-Fu-based schedule (up to the same total RT dose), followed by surgery and postoperative chemotheraphy. Adjuvant chemotherapy was allowed for patients in the RT-only arm, if in Stage III. Clinical outcomes significantly favored the combined treatment arm. The LCRTCT arm reported higher rates of R0 resections (84% vs. 68%; p = 0.009) and lower rates of local failure (67% vs 82%; p = 0.03). It failed to increase the OS although a trend was reported (66% vs. 53%; p = 0.09).

A RCT lead by north Europeans groups, defined by the acronyms “RAPIDO” trial, is currently enrolling patients presenting features of high risk features for local or systemic failure, including: cT4b, N2, MRF involvement, extramural vascular invasion. The protocol randomizes selected patients into a SCRT (25Gy in 5 fractions) followed by sequential preoperative chemotherapy (CT) and then surgery, or into a schedule of LCRTCT (1.8 Gy x 25 or 2 Gy x 25 with capetitabine) followed by surgery and then adjuvant CT with the same regimen of the first arm (but administrated for longer period). The primary objective of the study is to study the disease free survival at 3 years. The interest to compare such approaches in this subset of patients is to evaluate the potential of preoperative CT added to an RT schedule shorter than the common standard to both evaluate the potential wider use of SCRT, and to earlier deliver systemic therapy in patients at high risk for distant relapses. The aim of ongoing RAPIDO trial is to test if adding SCRT to sequential neoadjuvant chemotherapy can improve both the outcomes of survival endpoints, and the suboptimal rates of pathological complete responses (pCR) after preoperative treatment usually associated to SCRT.

For patients expressing adequate responses, the widest possible resection removing the initially infiltrated organs should be considered.

For selected presentation, intraoperative RT (IORT) or brachytherapy (BRT) is potentially indicated to improve outcomes.

**Resectable Tumors**

**Role of Postoperative Radiotherapy in the Clinical Integrated Management**

Historically, the adjuvant association of RT after surgery has been applied to improve clinical outcomes with encouraging results. The potential advantages of the availability of pathological staging to assess the need for further therapies to improve the clinical outcome following surgery, is the major point of strength for such approach.

At least 5 important randomized trials analyzed the impact of RT (not combined with chemosensibilization) after surgery. Even though none revealed a significant survival improvement, both the NSABP R-01 trials, and the MRC trials showed a significant improvement of local control over surgery-only arms. Some RCTs later confirmed the superiority of the concomitant use of radiochemotherapy (RTCT) in the adjuvant setting. Krook et al. did randomize 204 patients with rectal carcinoma (“either deeply invasive or metastatic to regional lymph nodes”) to postoperative RT alone (4500-5040 cGy) or to RT plus 5-Fluorouracil, which was both preceded and followed by a cycle of systemic therapy with 5-Fluorouracil plus Semustine (Methyl-CCNU).

The National Institutes of Health (NIH) Consensus Conference of 1990, stated the adjuvant use of RTCT after surgery for pT3 and/or N1-2 rectal cancers as standard in USA. In 1994 the RCT published by O’Connel et al. confirmed the use of protracted venous infusion (PVI) of 5-Fu concomitantly with RT after curative surgery; that became the standard association for adjuvant RTCT. In this four-arms randomized trial, 660 patients with locally advanced resectable rectal cancer received intermittent bolus injections or PVI of 5-Fu during postoperative RT. They also received systemic chemotherapy with Semustine plus 5-Fu or with 5-Fu alone in a higher dose, administered before and after the pelvic irradiation. Patients who received PVI 5-Fu (225 mg/m²/day; 7 days/week) had a significantly increased time to relapse (p = 0.01) and improved survival (p = 0.005).

Thus presenting potential advantages, and having showed a benefit over surgery alone, postoperative radiotherapy (either associated to chemosensibilization or not) have some drawbacks: the most important are related to the higher rates of toxicity respect to the preoperative setting, to the lack of induction of tumor response,
the potentially more radioresistant postsurgical bed due to more hypoxic tissues, and the need for wider radiation fields, to include the perineal scar, if surgery is performed by abdominoperineal resection (APR). Moreover a postoperative RTCT was shown to be unable to compensating for the presence of involved or threatened circumferential margins at surgery.\textsuperscript{24}

Two important randomized trials addressed that issue.\textsuperscript{25-27} The German Rectal Cancer Trial published in 2004 by Sauer et al.,\textsuperscript{25} enrolled more that 800 patients and randomized patients presenting T3-4 and/or N+ lesions (sited at less than 16 cm from the anal verge) to either preoperative RTCT (with PVI 5-Fu) versus postoperative RTCT. For patients in the arm undergoing preoperative treatment, they did found lower rates of local recurrences (6% vs. 13%; \(p = .006\)), and less acute toxicity (27% vs. 40%; \(p = .001\)), also late toxicity rates were lower (14% vs. 24%; \(p = .012\)). Moreover, authors reported a significant increase in rates of sphincter preservation (39% vs. 20%; \(p = .004\)) respect to the baseline choice by the surgeon to perform an APR.

They did not find any benefit for overall survival (OS) in one setting compared with the other (5-year OS: 74% vs. 76%). These results were later confirmed at an update with more than 10 years of median follow-up.\textsuperscript{26}

The NSABP R-03 trial randomized cT3-4 rectal cancers patients (after induction 5-Fu-based CT) to RTCT administered either preoperatively or postoperatively.\textsuperscript{25} The recruitment of 900 patients was planned, but only 267 were actually accrued (thus limiting the statistical power of the study).

Patients in the preoperative arm had significantly improved 5-year disease free survival (65% vs. 53%; \(p =.011\)) and a non-significant trend of improvement in 5-year OS (75% vs. 66%; \(p=0.065\)).

Rates of 5-year local control were similar in the 2 arms (11%).

Regarding toxicity: incidence of Grade 4 toxicity was more frequent in the preoperative arm (33% vs. 23%, mostly related to diarrhea); conversely, Grade 3 toxicity was less frequent (41% vs. 50%). Sphincter preservation’s rates improvement (on the basis of the baseline evaluation by the surgeon) (48% vs. 39%) was not observed in this trial.

As previously mentioned, also the selective use of postoperative RTCT to overcome an adverse postoperative presentations was shown to be inferior to the direct use of preoperative treatment.

In 2009 the UK Medical Research Council trial (MRC C07) randomized 1350 patients to preoperative RT (with SCRT administering 5 Gy x 5 fractions) or to selective postoperative RTCT (with LCRTCT administering 45 Gy at conventional fractionation plus concurrent 5-Fu based chemosensibilization).\textsuperscript{28} Postoperative LCRTCT was only provided to patients with histologic radical margins of less than 1 mm. With a median follow-up of 4 years, patients who received preoperative compared with selective postoperative treatment had significantly lower 3-year local recurrence rates (4.4% vs. 10.6%; \(p\leq0.0001\)) and higher 3-year disease free survival (77.5% vs. 71.5%; \(p = 0.013\)). It should be highlighted that this was not a trial meant to compare the SCRT to the LCRTCT approach, being the latter only applied for more adverse presentations, and in the sub-optimal postoperative setting.

On the basis of the evidences provided by these RCTs, the current standard of multimodal integrated approach to resectable rectal cancer is represented by the preoperative one, as summarized by International guidelines, the NIH recommendations about the use of postoperative RTCT stand in case of pT3 and/or N1–2 lesions.\textsuperscript{22-27}

**Role of Preoperative Radiotherapy in the Clinical Integrated Management.**

Preoperative radiotherapy, either in the SCRT or LCRTCT schedule, is the current standard approach to resectable (and marginally resectable) rectal cancer.\textsuperscript{11,28,2,10} The need for an adjuvant treatment integrating the suboptimal results of the surgery techniques around ’70 and early ’80\textsuperscript{24-30} has been already described in the previous paragraph: around ’90, in USA and part of the Europe, it lead to the choice of postoperative LCRTCT schedules. In the same period also some northern European Groups reported the positive impact on clinical outcome by adding preoperative RT (adopting the SCRT schedule) over surgery alone. In particular the Swedish Rectal Cancer Trial, published in 1997, not only confirmed a significant decrease in local recurrence rates (as for other previous similar experiences) but also gained a significant survival benefit over surgery alone.\textsuperscript{31}

They randomized 1168 patients with cT1-3 rectal cancer to receive or not 25 Gy (in 5 fractions of 5 Gy each) in 1 week, before undergoing surgery. The experimental arm showed significantly higher local control rates (12% vs. 27%; \(p <0.001\)) and an improvement in 5-year OS (58% vs. 48%; \(p = 0.004\)). An update after 13 years, did confirm the survival benefit (38% vs. 30%; \(p=0.008\))\textsuperscript{32}.

Among the over 10 randomized trials adopting SCRT (without concomitant chemotherapy) it remains the only one significantly affecting survival\textsuperscript{10,33}. Almost contemporarily, the North American experiences of LCRTCT, on the basis of some non randomized encouraging experiment of preoperative LCRTCT\textsuperscript{34}, were consolidating the use of preoperative approach. Later on, the developing of the new surgical approach represented by the total mesorectal excision (TME), first proposed by Heald and colleagues\textsuperscript{35-3}, radically improved the clinical outcome after surgery only. The local relapse rates were reduced of around 30% respect to the previous reports: the average 5 years local recurrence rates were about 5% \textsuperscript{136} questioning the need for neoadjuvant RT in itself (irrespective by the schedule adopted). The subsequent randomized trial published by Kapiteijn et al.\textsuperscript{36}, highlighted the benefit in term of local control although not on survival, derived by adding neoadjuvant radiotherapy even to an optimal surgical procedure. That multicenter randomized trial (commonly also known as “Dutch trial”) applied a certification of the quality for the surgery per-
formed in the study. The design of that trial faced TME-certified surgery alone to the same procedure preceded by neoadjuvant SCRT. Over 1800 patients presenting Stage II and III resectable rectal cancers were enrolled. The 2-year local control significantly favored the arm of integrated approach (2.4% vs 8.2%, p<0.001), while survival did not differ (82% vs 8.8%). On the other hand also the superiority of long course radiochemotherapy versus long course radiotherapy alone in the preoperative setting was confirmed by two randomized trials published in 2006, thus in “TME-era”\textsuperscript{37,38}. The European Organization for Research and Treatment of Cancer (EORTC) trial 22921 randomized over 1000 patients into 4 arms\textsuperscript{38}. Patients could have received preoperative RT up to 45 Gy (with conventional fractionation) with or without a concomitant 5-Fu-based CT, followed by surgery with or without adjuvant 5-Fu-based CT alone (i.e. RT→Surgery vs RT→Surgery+ CT Adjuvant vs RTCT→Surgery vs RTCT→Surgery+ CT Adjuvant). The arms administering LCRTCT reported significantly higher local control rates (8% to 10% vs. 17%; p<0.001) but no differences in the 5-year OS (65%), and similarly to other experiences, also at the updated report after 10 year of follow-up the evidence did not varied\textsuperscript{39}.

In the same year a less complex RCT performed by the Fédération Francophone de la Cancérologie Digestive (FFCD 9203) evaluated the same issue. They randomized 742 patients to either preoperative long course RT (delivering 45 Gy with conventional fractionation) with 5-Fu-based concomitant CT or to the same RT schedule without concomitant CT\textsuperscript{37}.

Like in the similar previous randomized experiment, reduced local failure rates (8% vs 17%; p<0.05) but no survival benefit (68% vs 67%) were reported.

It should be specified that even though both these 2 RCTs have been performed in the “TME-era” that was recommended but not mandatory thus performed in reduced percentages of the caisistics. Anyway one of the main issues investigated (i.e. the superiority of concurrent long course radiochemotherapy over long course radiotherapy alone) maintain its global significance.

Moreover an interesting parallelism in the finding of a significantly higher rate of pCR in the LCRTCT rather than in the RT only group was addressed by both these RCTs.

About the last RCTs mentioned, it is important to first of all highlight that the “Dutch trial" represents the evidence of significantly worth integration of surgery with RT in itself rather than an indication to the specific use of SCRT\textsuperscript{6}. Similarly the RCTs from Bosset \textit{et al.} and Gerard \textit{et al.}\textsuperscript{37,38} only represent the basis to remark the superiority of radiochemotherapy also in the preoperative setting when the long course approach is chosen: only RCTs directly comparing SCRT and LCRTCT have deepened the question on the schedule to be preferred.

The global evidence basis from the randomized trial reported seem to summarize that: the modern surgery for rectal cancer must be performed with a TME procedure\textsuperscript{38,3}; the integration of TME-surgery with radiotherapy is beneficial, in particular to improve local control and must be adopted in the preoperative setting to reduce toxicity and comorbidities\textsuperscript{6,62}. In the modern “TME era”, no randomized trial of multimodal approach, either SCRT or LCRTCT reported a survival benefit as single study: the best preoperative schedule to apply has to still be determined.

\textit{Definition of the optimal preoperative schedule of radiotherapy: Short Course Radiotherapy alone versus Long Course Radiochemotherapy}

As Bujko summarized in a review, there is still not enough evidence basis to determine what preoperative approach of RT is definitely superior between SCRT and LCRTCT. As Minsky highlighted in the same context, there are different reasons that lead to the two basic approaches of preoperative RT in the respective major areas of diffusion: SCRT in the north of Europe, and LCRTCT in USA and middle/South Europe\textsuperscript{6}. That include the trend of research that we described in the previous paragraphs: in USA the combined use of RTCT in the postoperative setting was shifted into the preoperative one by the evidences provided from RCT, whilst in northern Europe the administration of CT combined to RT was felt as more investigational, preferring to refer to different forms of intensifications of the biological efficacy (as by hypofractionation). The choice to enhance the different potentials of one or the other approach can address the schedule to prefer in routine practice or in specific situations (e.g. the higher protocol adherence or less clinical demand of SCRT versus the safe combination with chemotherapy or the potential of downstaging the lesion of the LCRTCT). Finally the different types of National recommendations could also play a role. All these differences are summarized by the certain range of differences among the recommendations reported by different National Guidelines\textsuperscript{6}.

As general consideration: the already mentioned randomized trials applying SC (Swedish trial or Dutch trial) or LCRTCT (German trial from Sauer \textit{et al.}) are not directly or indirectly comparable about results: first (obviously) because they did not randomize one approach versus the other, second, because patients selected for SCRT included patients with lower Stages (mostly cT1-3), while the vast majority of the patients accrued in the German trial had stage cT3 and/or N+\textsuperscript{10}.

Two RCTs directly compared SCRT to LCRTCT failing in revealing a definitive answer. The Polish trial from Bujko \textit{et al.} randomized 312 patients with cT3 rectal cancers to SCRT plus immediate surgery (i.e. 1 week later) versus LCRTCT with 5-Fu-based concomitant chemotherapy and delayed surgery (i.e.: 4-6 weeks after). No significant differences in local recurrence (14% vs. 9%), disease free survival (56% vs. 58%) and 4-year survival (66% vs. 67%) rates have been found.

Interestingly, the LCRTCT arm recorded an higher pCR rate (16% vs. 1%) and a lower incidence of positive radial margins (4% vs. 13%, p=0.017).
An Australian trial randomized 326 rectal cancer patients (cT3N+) to SCRT versus LCRTCT. Each arm administered postoperative chemotherapy. At a median follow-up of 5.9 years distant failure and overall survival rates did not differ.

Other randomized trials testing the same point are ongoing. A study from a German group (also named as "Berlin" Trial) will also include T2 N1–3 patients; adjuvant chemotheraphy will be mandatory for all the patients, and a high number of patients will be sought. The Stockholm III study is a three-arm RCT comparing long-course RT (without concomitant chemotherapy) with delayed surgery. SCRT with immediate surgery, and SCRT with delayed surgery. The last arm is intended to assess the potential of short-course radiotherapy to obtain pCR (mitigating one of the disadvantages of SCRT): in the published interim analysis the short-course arm followed by delayed surgery had 12.5% pCR compared with 0.8% in the SCRT arm with immediate surgery. Final results of the last 2 mentioned trials are still pending.

**Open Questions on SCRT and LCRTCT: how to improve their results?**

Final considerations about SCRT and LCRTCT should describe the approaches to improve each result by enhancing the respective potentials or reducing the disadvantages.

The Stockholm III trial tries to increase the pCR rates of SCRT by enlarging the delay before surgery: the achievement of pCR was widely reported as associated to significantly better survival outcome, a recent pooled analysis based on data derived from the major randomized trial also confirmed that, that is usually significantly more obtainable by the use of LCRTCT; moreover the excellent outcome for patient achieving a pCR lead to the experiences of wait-and-see policy of avoidance of surgery, with interesting preliminary results to be further evaluated in larger series. The interim results seem to confirm that, but it should be stressed that such results cannot be directly compared to the long course arm since that lacks the concomitant radiosensibilization in the Stockholm III. The RAPIDO trial was already mentioned, looking at the potential to combine SCRT with chemotherapy. On the other hand, researchers commonly applying LCRTCT try to enhance its potential to classically obtain higher pCR rates and reduce CRM+ by optimizing the concomitant drug association. In this direction attempts to include new drugs like Irinotecan or biological molecular targeted therapies like Bevacizumab in Phase I - II randomized trials reported conflicting results. New interesting issues were recently reported about the use of Cetuximab. The concomitant association of LCRTCT with Oxaliplatin was addressed over last years. Five randomized trials have examined the impact of addition of oxaliplatin to 5-FU or capecitabine based RTCT on response rates and acute toxicity in patients with cT3-4 and/N+ rectal cancer. With the exception of the German CAO/ARO/AIO-04, the other RCT showed increased acute toxicity without improvement of the pCR rates: the conclusion should be to not include oxaliplatin with conventional LCRTCT regimens, at least until definitive data on local control and survival will be available. Interestingly in one of these, the NSABP R-04, was also confirmed in randomized trial setting the non-inferiority of the use of oral Capecitabine instead of infusion 5-Fu.

Similarly to some SCRT new approaches, a sequential CT-administration was attempted into LCRTCT schedules. Garcia-Aguilar et al. performed a phase II randomized trial on 144 patients with cN+ rectal cancer. One arm administered preoperative RTCT (50.4 Gy + 5-Fu concomitant CT) followed by surgery (after 6 weeks), the experimental one administered the same preoperative schedule, but for patient presenting a clinical response, added mFOLFOX6 followed by surgery (11 weeks later). The pCR rate was increased in the mFOLFOX arm (25% vs. 18%) with no associated increase in postoperative complications (40% in each arm).

Lastly, the randomized trial INTERACT addressed the issue to intensify the biological effect by delivering a concomitant boost to the primary lesion rather that by intensifying the concomitant drug administration. The preliminary results confirmed an acceptable toxic profile for the concomitant boost arm, with a rate of pCR at the top boundaries of the literature reports.

**CONCLUSIONS**

Randomized trials reported the most important evidence basis currently available about the integrated management of rectal cancer tumors. RCTs also seem fundamental to summarize the more objective conclusions in term of shared standards of care, but also to address the future line of research for optimize survival outcomes. A recent pooled analysis performed of data derived by RCTs available confirmed the positive impact by preoperative radiotherapy into the integrated management of rectal cancer. This impact seemed stronger for patients achieving pCR (more frequently after LCRTCT). In the modern era, being available technical advantages like the learning models to elaborate data derived by large databases, and with an always increasing amount of new parameters upfront individuating the potential outcomes, or predicting response to therapies (like microRNA level or circulating tumor cells dosage, new molecular imaging modalities or elaboration of software-driven image data) it is important to refer to RCTs structured on rigorous basis, and keeping into account new surrogate endpoints to speed up the research processes.

**SUMMARY**

**ŠTA MOŽEMO NAUÈITI IZ RANDOMIZIRANIH STUDIJA O KARCINOMU REKTUMA I U ŠTA MOŽEMO VEROVATI**

Rezultati leëenja karcinoma rektuma su se znaèajno poboljšali u poslednjih skoro etedeset godina, zahva-ljuju u progresivnom razvoju novih integriranih terapijskih moguñosti.
Pa ipak, neophodna je optimizacija rezultata da bi se poveo još uvek sub-optimalni nivo preživljavanja. Nekolica nacionalna i međunarodna vodiča nude najbolje opcije tretmana na bazi procene podataka iz literature.

Međutim, još uvek postoji izvestan stepen neslaganja, posebno oko prednosti preoperativnog RT tretmana. Randomizirani trajali èine glavnu okosnicu i najvažnije sredstvo za nauèni scenari: definisati moguèe uspostavljanje standarda leçenja ili sugerirati najviše obeæavajuæe pristupe cilju istraživanja i u tom smislu usmeriti napore klinièara i istraèivaèa.

Ovaj rad je preteæno usmeren na rezultate iz randomizirane klinièke studije koja se odnosi na multimodalni integrisani tretman karcinoma rektuma. On je fokusiran uporedo na lokalno uznapredovali (LA) primarno nerevljanje standarda leçenja ili sugerirati najviše resektabilni (UR) i na resektabilni karcinom rektuma; bìæe navedene i izvesne relevantne ne-randomizirane studije.

Kljuèene reèi karcinom rektuma, kombinovani tretman, preopeprativna radiotherapija, hirurgija, postoperativna radiotherapija, hemoterapija

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