

Clinical Experience with Proton Therapy for Gastrointestinal Cancers: A Review

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ABSTRACT

Conventional radiotherapy (ie x-ray therapy) plays an important role in the multidisciplinary treatment of most of the cancers arising from the gastrointestinal (GI) tract. In this context, a narrow therapeutic window exists, due to 1) the usually large treatment volumes which are required to cover regions at risk for tumor spread and to 2) the close vicinity of several radiosensitive healthy tissues to the irradiated volume. The use of charged particles such as protons, with their unique dosimetric characteristics (a finite range in tissue along with a near zero dose beyond the end of its path), could be promising. The aim of this critical review was 1) to describe the rationale of the use of PT for the major GI cancers and 2) to report the clinical experiences currently available in literature.

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Key words: Protontherapy; Gastrointestinal cancers

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INTRODUCTION

Gastrointestinal (GI) cancers (affecting organs within or functionally related to the alimentary tract) are common cancers, both in developed and less developed countries. In 2008, tumors of five major sites (esophagus, stomach, pancreas, liver and colorectum) have been estimated to affect >2,000,000 people causing more than 1,600,000 deaths worldwide^[1].

Tumor characteristics such as localization and stage along with goal of treatment (curative vs. palliative) drive the choice of the proper oncological strategy, which is responsibility of a multidisciplinary team (including medical oncologists, surgeons and radiation oncologists).

Radiotherapy can be administered, with or without concomitant chemotherapy, as an adjuvant treatment (before or after surgery) or as a radical, definitive option.

The administration of conventional radiotherapy (i.e. X-ray radiotherapy) in GI tumors is often complex, due to (1) the usually large treatment volumes which are required to cover regions at risk for tumor spread^[2,3] and (2) a narrow therapeutic window caused by the presence, close to the irradiated volume, of several healthy organs whose tolerance to radiation is well below the dose required for an effective treatment^[4].

Protons are charged particles with unique dosimetric characteristics of a finite range in tissue along with a near zero dose beyond the end of its path, allowing for a better sparing of normal tissues in the range of medium-low doses^[5]. The total energy deposited to the body (i.e. integral dose) is also reduced in comparison with photons with a potential reduction of secondary malignancies^[6].

The use of protons for medical purposes was described for the first time by the American physicist R. Wilson in 1946 in a landmark manuscript^[7].

Nowadays, there is a growing interest in the oncological community on the medical use of protontherapy (PT); as of 2012, 36 PT centers are operating around the world, with a 30% increase since 2005. It is estimated that more than 50 PT facilities will be

active at the end of 2014^[8].

There is plenty of debate in literature between pros, cons and cost-effectiveness of the widespread adoption of PT^[9-11].

Moreover, many variables can influence the precision and reliability of a radiotherapy plan, and even more of a PT plan: anatomical changes (inter and intra fraction), set-up error, delivery/imaging misalignment, etc.^[12]. Motion is definitely a major technical problem in PT^[13]. All these issues must be taken into account in radiation treatment for GI malignancies.

Several, non-clinical studies described the dosimetric advantages of the use of PT in GI cancers^[14,15].

In the present review, we aimed (1) to describe the rationale of the use of PT for the major GI cancers and (2) to report the clinical experiences currently available in literature.

ESOPHAGEAL CANCER

In 2008, esophageal cancer accounted for 3.8% of all new cancer cases worldwide, representing the sixth most common cause of death from cancer^[1].

The standard treatment for locally-advanced disease is neoadjuvant radiochemotherapy followed by surgery, which improves survival compared with surgery alone (median survival 49.4 months vs 24 months), as shown recently in a phase III trial^[16].

Radiotherapy is usually administered up to a dose of 45-50 Gy to large volumes to cover possible areas of microscopic tumor spread along the esophageal mucosa. The risk of severe acute and late toxicity is not negligible due to the close vicinity of numerous healthy organs at risk (OAR) such as lungs, spinal cord, heart and esophagus itself. Postoperative complications, mainly pulmonary and GI, can also occur: they can be decreased with the use of advanced radiation techniques such intensity modulated X-ray radiotherapy (IMXT) or PT, as demonstrated by the study of Wang *et al.*^[17] Dose intensification schemes (up to 64.8 Gy delivered to the macroscopic tumor) failed to reveal a clinical benefit^[18]. Recent, retrospective studies, showed that most of local failures occur in the region of primary tumor^[19]; however, the feasibility of further dose-escalation protocols for definitive radiochemotherapy is limited by the risk of late esophageal toxicity.

In this context, PT could be used to reduce the amount of acute and late, non-esophageal toxicities as well as postoperative complications; its integration in novel chemotherapy regimens could also be tested.

The clinical experience in PT and esophageal cancer comes from USA (MD Anderson Cancer Center) and Japan (University of Tsukuba)^[20-23].

In the series from Japan, PT was delivered mostly as a boost to the primary tumor after an initial X-ray treatment to larger volumes: doses up to 90 Gy were achieved with 5-year overall survival and local control rates of 21.1 and 38%, respectively^[22]. No concomitant chemotherapy was given.

Lin *et al.*^[20] firstly reported the use of concomitant PT and chemotherapy for esophageal cancer: 62 patients treated between 2006 and 2010 with different intents (adjuvant, neoadjuvant or radical) were retrospectively reviewed. Median dose was 50.4 Gy (range 36-57.6 Gy). The estimated 3-year survival was 51.7% with a loco-regional control of 56.5%. The pathological complete response in patients undergoing surgery was 28%. Moderate treatment related toxicities were generally observed (G3 dysphagia and esophagitis rates <10%); however, two G5 toxicities were observed (one cardiac arrest and one presumed radiation pneumonitis). A low rate of postoperative complications (pulmonary, cardiac, GI and wound infection) was also experienced (each less than 10%).

GASTRIC CANCER

Stomach cancer is the fourth most common neoplasm worldwide and the sixth in developed countries; as of 2008, it represents globally the second leading cause of death from cancer in both sexes^[1]. Surgery is the mainstay of cure for this disease; however, randomised phase III trials of adjuvant therapies have shown a significant impact on survival compared to surgery alone^[24,25]. In the context of chemoradiation, the Intergroup 0116 study^[24] showed a significant gain in both median overall and relapse-free survival in patients undergoing adjuvant treatment compared with those who received surgery alone. A recent update of this trial confirmed the persistent advantage of multimodal treatment over surgery alone at a median follow-up of more than ten years^[26].

Toxicity of chemoradiation is significant as 17% of patients on the INT 0116 trial discontinued treatment, with 9% of patients receiving less than 40 Gy; one percent of patient population died for treatment-related fatal complications. A non-significant increase in the occurrence of second malignancies was also reported in the chemoradiation arm^[26]. Other studies also reported data on late toxicity, mainly to kidneys and bowel^[27,28].

In the context of radiotherapy, the historical field arrangement used in most of the patients in the INT 0116 study consisted of two parallel opposed anteroposterior/posteroanterior (AP/PA) fields; anatomical limits were usually contoured on simple simulation films^[29].

Compared to AP/PA arrangement, more advanced techniques such as 3D conformal radiotherapy (3DCRT) and IMXT have been shown to provide better coverage of target volume and improved OAR sparing^[30,31].

Similar or even better results could be achieved with the use of PT with a possible gain in acute and long-term toxicity to healthy OARs such as kidneys, small bowel and heart. The clinical literature is limited to case reports from University of Tsukuba, Japan^[32,33]. High doses (61-86 Gy) were delivered to unresectable patients with good results in terms of local control. No planning comparison studies are available.

PANCREATIC CANCER

In 2008, more than 138,000 new diagnoses of pancreatic cancer were expected^[1]. As known, prognosis is poor with 5-year overall survival rate less than 10%.

Surgery with radical resection (R0) is essential for cure with a 5 year survival of around 20%^[34]; however, it can be performed in the minority of patients with pancreatic cancer. Local and distant failures after surgery are common^[35]. A recent landmark study from Iacobuzio-Donahue *et al.*^[36] showed that uncontrolled local growth is the cause of death in 30% of patients; the study suggested that genetic status of pancreatic carcinoma (i.e. loss of Dpc4 expression) could predict widespread metastatic failure.

Adjuvant chemotherapy (5-FU or gemcitabine based) improves survival compared with surgery alone^[37,38] and it is universally accepted as a standard of care. Conversely, the usefulness of the addition of radiotherapy in the adjuvant treatment of pancreatic cancer is passionately debated. The Northern American oncological community strongly believes in the safety and effectiveness of chemoradiation on the basis of the positive results of both prospective and retrospective studies^[39,40]. On the other hand, in Europe the negative results of the phase III ESPAC-1 trial^[41] make oncologists more skeptical regarding adjuvant chemoradiation. It must be said that the trial design and execution generated a lot of controversy^[42]; it is desirable that current ongoing trials^[43] would

definitely demonstrate the positive impact on survival of adjuvant chemoradiation in pancreatic cancer.

The use of standard dose (50.4 Gy in 25 fractions) radiotherapy in combination with chemotherapy (gemcitabine) improves survival in unresectable patients at a cost of increased G4 toxicity, as shown by Loehrer *et al.*^[44]. Dose escalation schemes (up to 55 Gy in 25 fractions) delivered with IMXT in combination with gemcitabine revealed good results in terms of local control (59% at 2 years) with 24% rate of severe toxicity (mainly GI and nutrition disorders); moreover, 24% of patients were able to undergo resection with favorable outcomes^[45].

Border-line resectable cancer can also benefit of neoadjuvant radiochemotherapy in order to allow radical surgery^[46].

In this context, PT could allow for a reduction in acute radiation-related toxicity, leading to (1) a better compliance to standard chemoradiation regimens; (2) an intensification of radiation delivered dose; and (3) a potential safe administration of novel radiosensitizers, with the ultimate goal of improving the poor survival rates of this disease.

Several dosimetric studies demonstrated the better OAR sparing that can be achieved with PT^[6,47] in comparison with X-ray therapy.

Clinical studies were conducted in USA and Japan. Hong *et al.*^[48] reported the results of a Phase I study of preoperative chemoradiation for localized head pancreatic cancer: a fractionation scheme consisting in 5 fractions of 5 Gy (delivered daily from Monday to Friday) was considered as the maximum tolerated dose schedule. Eleven patients underwent resection; radical (R0) surgery was performed in nine patients.

Nichols *et al.*^[49] retrospectively reported the use of PT with concomitant capecitabine in 22 patients treated with different intent (adjuvant, $n=5$, marginally resectable, $n=5$, unresectable, $n=12$) between 2009 and 2012. Radiation doses ranged from 50.4 Gy to 59.4 Gy. No $\geq G2$ toxicities were observed. In the latest patients, no $\geq G2$ GI toxicity by avoiding anterior and left lateral beams and by using one-two posterior beams in association with a low-weighted right lateral beam. Of note, two patients initially considered inoperable registered a significant response to treatment and underwent pancreaticoduodenectomy.

Terashima *et al.*^[50] from the center of Hyogo conducted a phase I-II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer. After an early phase, patients ($n=40$) were treated with a highly hypofractionated regimen (67.5 Gy in 25 fractions using the field-within a field technique to deliver 2.7 Gy daily to the PTV non-adjacent to GI tract) concomitant with full-dose gemcitabine. Local control and overall survival at 1 year were 82% and 77%, respectively; the most frequent acute toxicities were neutropenia, anorexia and weight loss. The major $\geq G3$ late toxicity was gastric hemorrhage with ulcer, which occurred in four (10%) patients, with a fatal (G5) event. Interestingly, a recent study from the same Institution aimed to evaluate the rate of upper GI complications occurring immediately after the completion of the above-mentioned treatment regimen. By gathering and analyzing data from pre- and post-treatment endoscopies performed in 91 patients, the authors registered a high (49.4%) rate of radiation-induced ulcers (scored as G1), mainly located in the lower part of the stomach and in the horizontal part of the duodenum. Neither GI hemorrhage nor perforation were found at the time of post-treatment endoscopy.

HEPATOCELLULAR CARCINOMA

Primary liver cancer is the third cause of death from cancer worldwide^[1], with a growing incidence in Europe and in the United

States in the last decades^[51]. Hepatocellular carcinoma (HCC) stands for 90% of all liver cancers; in most cases, HCC is associated with an underlying chronic liver disease developed in the presence of well known risk factors such as viral hepatitis, alcohol abuse and exposure to aflatoxines^[52].

Cancer progression, mainly loco-regional progression is the cause of the majority of deaths in HCC population^[53]; the rate of extrahepatic metastases, indeed, is limited even in patients with advanced, unresectable HCC^[54]. Surgery (partial liver resection or liver transplantation) is the mainstay in the treatment of HCC, with a reported rate of survival at 5 years greater than 70% in selected series^[55]. The percentage of HCC patients suitable for surgery however is limited by both tumor and patient-related contraindications.

Other therapeutical approaches for localized HCC consist of ablation with percutaneous ethanol injection (PEI) or, more recently, radiofrequency ablation (RFA), which represents an effective option for small HCCs not suitable for surgery^[56]. The rate of recurrence in the ablation site, however, is not negligible, especially for tumors larger than 3 cm^[57].

The role of radiotherapy in the treatment of HCC is still under debate. No clear consensus exists between international guidelines^[58,59]. The low radio-tolerance of liver and the need of high doses of radiation for disease control, indeed, narrow the therapeutic window for a safe and effective treatment. Furthermore, irreversible hepatic failure is a frequent and frightening consequence of radiation-induced liver disease (RILD)^[60].

The rationale of the use of PT in primary liver cancer lays in the physics peculiarities of protons, which allow for a better sparing of organs at low and medium doses if compared with photon radiotherapy. These properties fit well with irradiation of the liver: its tolerance to radiation, as a parallel arranged organ, is strongly correlated to the mean dose and to the volume of organ which can be spared to a certain amount of radiation^[60].

In general, comprehensive reviews concerning the use of PT in cancer revealed a potential benefit for HCC patients^[61]. In addition, our group conducted a systematic review of the published reports in the period 1985-2012^[62]. More than 900 HCC patients received PT in the selected studies. The eight clinical studies analyzed a heterogeneous group of patients presenting various levels of underlying liver function and bearing single or multinodular HCCs of different sizes. The results of the retrieved studies (Table 1) are encouraging: a high and long lasting LC, greater than 80% at 5 years, is achievable with the use of PT for HCC. Data on survival are impressive with rates comparable to surgery in the most favourable groups; good outcomes can be observed also in poor prognosis patients, such as the 30% survival at 5 years for stage C disease in the series from Hyogo. Proton therapy was considered a well-tolerated treatment in all the reported series; skin-dermatological and GI toxicity represented the most frequent reported adverse events. The low quality of the retrieved studies (i.e. the scarcity of prospective studies) drives down without wiping out the interest towards the impressive clinical results registered in several stages of disease.

ANO-RECTAL CANCER

As of 2012, rectal cancer is the second most common cancer of the digestive system diagnosed in USA^[63]. Prognosis is good, with 5 year relative survival of 70/90% for regional/localized disease (data from colon and rectal cancer combined)^[64].

Standard treatment consists of neoadjuvant 5-FU-based chemoradiation (50 Gy in 25-28 fractions) followed by surgery with

Table 1 Main results of the selected studies adopting PT for HCC patients.

Center	Treatment regimen	N° of patients	Clinical results	Local control	Overall survival	Toxicity	Remarks
PMRC	TD=72Gy dpf=4.5 Gy, TD=78 Gy dpf=3.9 Gy TD=84 Gy dpf=3.5 Gy, TD=50 Gy dpf= 5 Gy miscellaneous regimens=97 T	162	86.9% at 5 y for all T	83.3% at 5 for peripheral, single T	23.5% at 5 y 53.5% at 5 y for CP A and single T	Acute = 9.7% ↑ transaminase level (autoresolving). Late=Infection biloma (1.1%), Biliary duct stenosis (0.5%), GI bleeding (1.1%)	9% of pts received >1 course of PT. 85% of pts developed another HCC in the liver, LC and OS not affected by TT, OS significantly affected by CP score and n° of T
PMRC	T ≤2cm from GI tract TD=77Gy dpf=2.2 Gy (65 pts) Peripheral T TD=66 Gy dpf=6.6 Gy (104 pts) miscellaneous regimens=64 pts	318	83.3% at 5 for peripheral, single T	44.6% at 5 y for all pts (55.9% at 5y CP A pts, 44.9% CP B pts) P<0.01	3 (1.2%) G2 GI toxicity 1 pt G3 GI tox. (→surgery) 3 rib fractures 28 G2 skin toxicities	19.8% of pts received > 1 course of PT OS better with PTV<125mL, P<0.05	
HIMBC	TD=76Gy dpf= 2 Gy (11 pts) TD=56 Gy dpf= 7 Gy (4 pts) TD= 60 Gy dpf= 6 Gy (89 pts) TD= 76 Gy dpf= 3.8 Gy (70 pts) TD= 66 Gy dpf= 6.6 Gy (53 pts) TD= 80 Gy dpf= 4 Gy (3 pts) TD= 84 Gy dpf= 4.2 Gy (3 pts) TD=52.8 Gy dpf=13.2 Gy (9 pts)	242	90.2 % at 5 y for all pts 84.1 % at 5 y for T ≥5 < 10 cm	38% at 5 y for all pts 67.6% at 5 y for operable group 30.6% at 5 y for BCLC stage C pts	≥G3 late toxicities in 8 pts 1G4 dermatitis 4G3 dermatitis 1G3 biloma 1G3 pancreatitis 1G3 GI ulcer IRILD 8 G2 rib fractures	LC significantly affected by T size, OS at 5 y for pts treated with BEID10 <100 vs ≥100=31.7% and 43.9%(P=NS), OS significantly affected by PS, CP score, presence of macroscopic vascular invasion, The majority of skin and chest wall toxicity in the early period of the study	
NCCHE	TD= 76 Gy dpf= 3.8 Gy TD= 60 Gy dpf= 6 Gy (3 pts) TD= 65 Gy dpf= 2.5 Gy (11 pts)	60	LPTS at 3 y= 90% (all pts), LPPS at 5 y= 86% (all pts), LPPS at 3 y for pts receiving 76 Gy vs those receiving 62.5 Gy=97% vs 56% (P=0.005), 61% radiological CR at 1 to 50 m after PT	OS at 3 y= 56% (all pts) OS at 5 y= 25% (all pts)	PHI in 11 pts, all with ICG R15>20%, 7 deaths (5 without recurrence) 3 ≥G2 GI toxicities, 1 duodenitis 1 colon ulcer, 1 esophagitis	9 out of the 32 intrahepatic recurrence occurring in the same portal segment V30 and ICG R15 suggested as potential predictors of liver toxicity ICG R15 >50% = NO PT	
WPTC	TD ranging from 52 Gy to 72 Gy in 13-28 f, dpf= 2-4 Gy	39	Stage I-II= 94.1% at 1 y, CR 35.3% at 6 m	Stage I-II= 88.2% at 1 y	No > G1 skin tox 1 pyloric obstruction	2 deaths in CP C pts (1 liver failure, 1 hemorrhage and distant metastasis)	
NCC	HCC free from GI tract TD=60Gy dpf=3 Gy (8 pts) (dose level 1) TD=66 Gy dpf=3 Gy (7 pts) (dose level 2) TD=72 Gy dpf=3 Gy (12 pts) (dose level 3) HCC close to GI tract TD median 66 Gy (range 44-66) dpf= 2.2,5,3 in 20-22 f HCC with PVTT TD= 50 Gy dpf= 2.5 Gy (7 pts) TD= 55 Gy dpf= 2.5 Gy (18 pts) 1 pt= TD and dpf not reported	HCC free from GI tract= 27 HCC close to GI tract= 29 HCC with PVTT= 26	HCC free from GI tract CR= 62.5%, 57.1% and 100% in dose levels 1,2 and 3, respectively LPPS at 3 y=71.4%, 85.7% and 82.5% in dose levels 1,2 and 3, respectively Overall LPPS at 3 y= 80.5% HCC close to GI tract LPPS at 3 y= 63% HCC with PVTT P=CR+PR 73.1%, PVTT=CR 57.75%	HCC free from GI tract OS at 3 y=25%, 47.6% and 70.7% in dose levels 1,2 and 3, respectively (P=NS) Overall OS at 3 y= 56.3% HCC close to GI tract OS at 3 y= 39% HCC with PVTT OS at 2 y= 33.6%	HCC free from GI tract No ≥ G3 acute toxicities HCC close to GI tract 1 G2 gastric ulcer HCC with PVTT 3 G2 non hematologic toxicities	HCC free from GI tract CR significantly higher in dose level 3 OS at 3 y CR vs Non-CR= 62.9% vs 33.3% (P= .075) Recommended dose for HCC free from GI= 72 Gy in 24 fr HCC close to GI tract LC and OS not affected by TT	
MGH	TD ranging from 52.5 Gy to 75 Gy in 15 fractions	14 (11 HCC)	100% at 1 y	mDFS for all T= 12 m	1 G3 GI bleeding 1 G3 bilirubinemia 1 G5 stomach perforation no RILD	The study included 11 HCCs, 3 HCC and one liver metastasis (separate data not reported)	
LLUMC	TD= 63 Gy dpf= 4.2 Gy (76 pts)	76	80% at 5 y	PPS for patients within Milan criteria= 60% at 3y PPS for patients within Milan criteria= 20% at 3y 70% OS for transplanted pts	5 G2 GI toxicities No RILD	The Milan Criteria significantly affected survival at multivariate analysis. pCR in 33% of transplanted pts	

PMRC: Proton Medical Research Center, Tsukuba, Japan; HIMBC: Hyogo Ion Beam Medical Center, Japan; NCCHE: National Cancer Center Hospital East, Chiba, Japan; WPTC: Wanjie Proton Therapy Center, Zibo, China; NCC: National Cancer Center, Ilsan, South Korea; MGH: Massachusetts General Hospital, Boston USA; LLUMC: Loma Linda University Medical Center, USA; TD: total dose; dpf: dose per fraction; T: primary tumor; y: years; CP: Child-Pugh score; GI: gastrointestinal; PT: proton therapy; LC: local control; OS: overall survival; pts: patients; tox: toxicity; PTV: planning target volume; BCLC: Barcelona Clinic Liver Cancer; RILD: radiation induced liver disease; BEID: biological effective dose; NS: not significant; LPPS: local progression free survival; DFS: disease free survival; ICG R15: indocyanine green retention rate at 15 minutes; PHI: proton hepatic insufficiency occurring within 6 months after PT.

Total Mesorectal Excision and adjuvant chemotherapy^[65]. Short-course radiation (25 Gy in 5 fractions) followed by immediate (within one week) or delayed (>4 weeks after the completion of radiotherapy) surgery is also performed^[66,67]. Intensification of chemotherapy by the addition of a second drug (i.e. oxaliplatin) failed to demonstrate a local benefit^[68].

Radiation related toxicity is not negligible in rectal cancer patients: severe acute and late toxicities affect various OARs such as small bowel, bladder, bone marrow, bony structures, nerve roots, reproductive and sexual apparatus^[65,69-71]. Moreover, occurrence of second tumors is increased compared with surgery alone^[72].

Quality of life for these patients, which in most cases are long survivors, is decreased compared to general population^[73]. Several studies are currently evaluating the possibility to avoid upfront radiotherapy in selected patients^[74].

Thus, improvements in radiotherapy administration are compulsory, with the aim to (1) further improve the clinical outcome (i.e. in T4 cancers); (2) decrease the negative impact of radiotherapy on patients' quality of life. In this context, advanced X-ray therapies, such as IMXT, have been recently implemented in rectal cancer treatment with promising results^[75].

The superior dose distribution of protons is confirmed by dosimetric analyses on rectal treatment volumes^[76]. PT could be useful for: (1) reduce treatment related acute and late toxicities; (2) reduce the incidence of treatment-related second cancers; (3) evaluate chemotherapy intensification schemes in order to decrease the rate of distant failures; and (4) evaluate radiation intensification schemes maintaining an acceptable profile of toxicity with the multiple goals of increasing local control in very advanced disease, increasing sphincter-sparing surgeries in low rectal cancers, or even omitting surgery in complete responders^[77].

However, clinical literature is scarce^[78].

A similar approach could be tested in anal cancer, a relatively rare tumor^[63] with an excellent prognosis (5-year survival of 80% in localized disease)^[79].

The standard approach, since the landmark work of Nigro *et al.*^[80], is chemoradiation with curative intent. Surgery (Miles' operation with abdominoperineal resection and a definitive stoma) is reserved for non-responding patients. Radiation doses are usually higher (54-59 Gy) compared with those delivered for rectal cancer. Larger treatment volumes (including external iliac and inguinal node regions) are also irradiated. Treatment related toxicities are frequent and could prolong total treatment time potentially affecting patients' outcome^[81]. Likewise, long-term treatment related morbidities occur frequently^[82].

The Radiation Therapy Oncology Group 0529 trial^[83] aimed to investigate the potential benefit of the use of IMXT in anal cancer: even if the primary end-point (15% reduction of combined genitourinary and GI toxicities compared with 3D conformal radiotherapy) was not met, a significant decrease in G2 hematological, G3 GI and dermatological acute adverse events.

It would be remarkable to investigate if PT could achieve better clinical results than advanced IMXT.

Again, clinical literature is limited^[78].

FINAL REMARKS

Report n° 78, which the International Commission on Radiation Units and Measurements (ICRU 78) dedicated to proton therapy, suggests that "the dose-sparing possible with protons is likely to be most valuable for large target volumes for which sparing the

remaining volume is likely to be particularly valuable"^[84]. This is often the case of GI cancer radiotherapy. Moreover, the number of GI cancer patients potentially eligible for PT is high^[85,86].

However, the administration of GI radiotherapy is complex, and even more issues are involved in PT treatment^[87,88]. Thus, the clinical experience is still scarce. Most of the studies regarding the use of PT in GI cancer treatment focused on HCC and reported good outcomes. A survival benefit could also be achieved in pancreatic cancer. A potential benefit can be presumed in all other malignancies by the reduction of treatment -related toxicity with a possible improvement in cancer survivors' quality of life. Several trials are currently ongoing such as NCT00976898, NCT00857805 (HCC) NCT01683422, NCT01553019 (Pancreatic cancer), NCT01512589 (Esophageal cancer) and NCT018580259 (Anal cancer). A positive outcome of such trials would endorse the role of PT as an effective option in the local treatment of GI malignancies.

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