Patterns of radiotherapy practice for pancreatic cancer: Results of the Gastrointestinal Radiation Oncology Study Group multi-institutional survey

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Abstract. No information is currently available regarding pancreatic cancer (PC) pattern of care in Italy. In the present study, a nationwide survey using a questionnaire was performed to enquire the local standards for PC diagnosis and radiotherapy treatment. Fifty-seven percent of 140 Italian centres completed questionnaire. The main causes of no radiotherapy indication were poor general condition (45%) and lack of guidelines (25%). Physicians (38%) employed neoadjuvant therapy in locally advanced PC patients, while in other centres (62%) adjuvant chemoradiation was administered. Adjuvant gemcitabine-based chemotherapy was selected as the treatment of choice by 59% of centres. Patients were treated mostly with doses of 50-54.9 Gy on the tumour (or bed) plus lymph nodes. A 3D-CRT technique was used in 81.2% of centres, while IMRT and IGRT were available in 61.2 and 48.7% of cases, respectively. Extensive variation exists with regard to patterns of care for PC in Italy. Nevertheless, cooperative studies emerging from this survey appeared beneficial.

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-associated mortality in the European Union, being the only major cancer site for which no improvement in mortality rates is predicted for both genders. By contrast, a slight increase in mortality rates is expected (1).

Surgical resection is the only curative therapeutic modality with a 5-year postoperative survival rate of ~10-15%. However, only ~20% of patients are diagnosed with surgically resectable PC, 40% of patients have metastatic disease and the remaining 40% have locally advanced PC in the borderline resectable or unresectable advanced PC form.

Therefore, PC poses a challenge to oncologists and, in particular, controversy surrounds radiation oncology (RO) in the management of PC. Advances in the field of RO have led to improvements in imaging and targeting as well as radiation treatment delivery. Although these advances have the potential

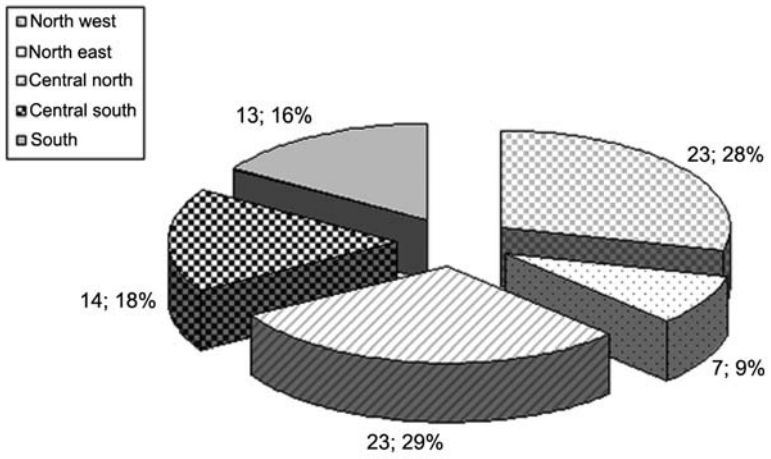

Figure 1. Number and percentages of participating Radiation Oncology Centres according to major Italian geographic areas (North East, North West, Central North, Central South, South and Islands).

to increase tumour control and decrease toxicity, to the best of our knowledge, randomized clinical evidence supporting their widespread application does not exist and there is still a great variety in patterns of practice in different regions worldwide.

Patterns-of-care studies, initially developed in the US in the mid-1970s, are a reliable retrospective study design used to establish the national practice for cancer patients during a specific study period (2,3). Patterns-of-care surveys on PC were conducted in Germany (4), Japan (5,6) and the USA (7). However, to the best of our knowledge, in Italy, no information is available on national RO approach to pancreatic neoplasm.

In the present study, the Italian Society of Radiation Oncology Gastrointestinal Cancer Study Group (AIRO-GI) conducted a nationwide survey among radiation oncologists investigating the clinical practice of PC diagnosis and treatment in Italian university and community hospitals with the aim to subsequently be, proactive in suggesting collaborative multicentre trials. To the best of our knowledge, this is the first report to establish the manner in which RT is used in the treatment of PC in Italy.

Materials and methods

Survey design and questionnaire. The study questionnaire was designed by AIRO-GI members in September 2013. The main goal of the questionnaire was to enquire into the local standards for PC diagnosis and RT treatment at the participating centres. Data selected and assessed were from 2012.

The questionnaire, consisting of 40 items, was grouped in four sessions: i) data of the participating physicians: professional site (e.g., university or community hospital, private practice), number and type of PC patients treated per year (2012), work methods (presence or absence of multidisciplinary group), indications for RT and applied techniques [3D conformal RT (3DCRT), intensity-modulated RT (IMRT), image-guided RT (IGRT), intraoperative RT (IORT), stereotactic RT (SBRT), brachytherapy (BRT)]; ii) questions on the local standard diagnostic procedures for PC and issues concerning the histological type; iii) queries concerning the RT treatment standard for resectable (including neoadjuvant and adjuvant therapy) and advanced PC, as well as dose and fractionation details according to treatment modality; iv) questions on RT technical aspect (immobilization systems, use of contrast, gating systems, image fusion), and intention of the individual centres to join multicentre trials. The multiple-choice and open questions were part of the survey.

Participating physicians. The participating centres were not pre-selected. From November 2013 to January 2014 the questionnaire was proposed by the AIRO-GI to all 140 Directors of the Italian Radiation Oncology Institutions as per AIRO website (www.radioterapiaitalia.it: update as per November 2013).

The study methodology was focused on the division of the Italian territory in major geographic areas (North East, North West, North Central, South Central, South and Islands) and the identification for each of them of a radiation oncologist responsible for soliciting and collecting questionnaires via e-mail.

Statistical analysis. Returned questionnaires were collected centrally at the Fondazione 'Giovanni Paolo II'-UCSC, Campobasso and data were entered into an electronic database. The data processing in collaboration with the Institute of Statistics of Aviano occurred in the first six months of 2014. Study data were analyzed by SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

Eighty questionnaires, accounting for 57% of the 140 Italian centers available on the AIRO website were completed and returned. The responding centres were evenly distributed in five major areas identified with a predominance of the north-central part and reflected the distribution of RT centres throughout the country (Fig. 1).

Session 1. Most of the participating physicians came from community hospitals (N=58), followed by private (N=12) and university hospitals (N=10).

Only 5% of RT services did not treat PC patients, due to the following reasons: i) patients were referred to a reference centre for pancreatic neoplasm; ii) patients were recorded into

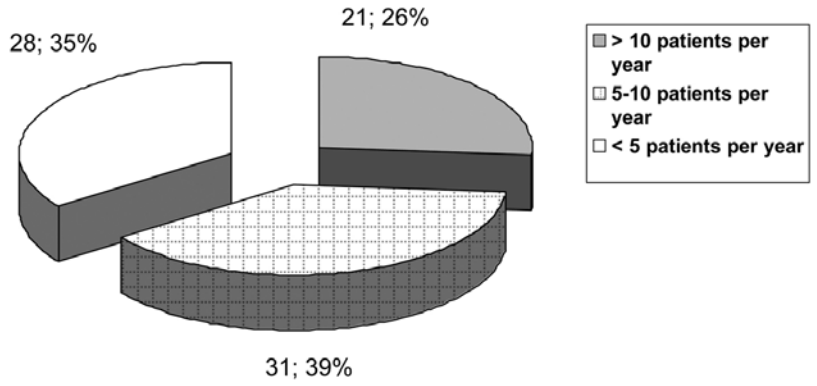

Figure 2. Stratification of participating Radiation Oncology Centres according to the number of treated patients per year (2012).

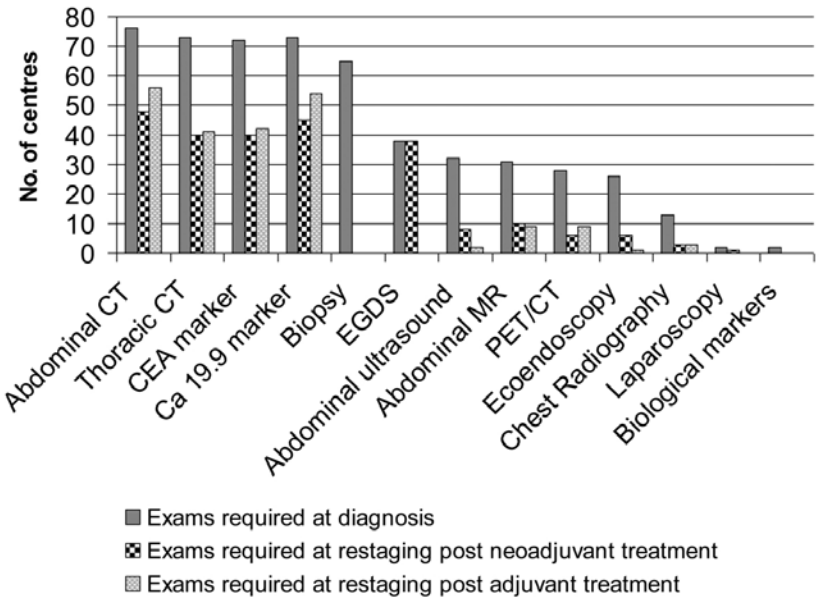

Figure 3. Diagnostic examinations required for PC staging (grey bar) and restaging after neoadjuvant (black and white bar) or adjuvant treatment (pale grey bar).

the Hospital (Surgery or Medical Oncology services) but were not addressed to a radiation oncologist.

The majority (95%) of radiation oncologists evaluated PC cases. The main causes of no RT indication were poor general condition/co-morbidities (45%), lack of guidelines (25%), inadequate timing (e.g., time elapsed from surgery) (10%), excessive waiting list (4%), internal policy (4%), inadequacies of the centre (e.g., lack of day hospital or inpatient treatment for the management of acute complications) (4%), patient's age (4%) and prior systemic therapy (4%). The absolute figure of PC patients treated in 2012 was 568, although this number did not reflect the reality as only 57% of Italian centres replied to the questionnaire, and of those only 69% of centres participating in the survey provided the absolute number of irradiated patients. Stratification in groups according to number of treated patients per year (2012) is shown in Fig. 2. A tumour board for PC was reported by 63% of participating centres, including 'always' a surgeon, a radiation and a medical oncologist (100% of cases), often a radiologist (80%) and an endoscopyst (80%), sometimes a nuclear medicine physicist (36%), a pathologist (40%), a physician nutrition specialist (32%) and a pain therapist (26%). The tumour board meeting was periodic in approximately two third of cases, while upon request in the the remaining third of cases.

Radical pancreatectomy procedure was mostly performed in the same centre in 59% of cases, while in other neighbouring health facilities or in Italian referral centres in 23 and 18% of cases, respectively. IORT was performed exclusively in six centres with <5 patients/year in 2012.

Session 2. Fig. 3 shows the diagnostic examinations as required by the different RO units for PC staging and restaging following neoadjuvant or adjuvant treatment. In particular, at the time of diagnosis, thoracic and abdominal CT (91 and 95%, respectively) as well as biopsy and marker determination (81 and 91%, respectively) were performed in the majority of patients. Esophageal-gastroduodenoscopy (EGDS), abdominal ultrasound, abdominal magnetic resonance (MR), PET/CT, ultrasound endoscopy and laparoscopy (LPS) were considered less mandatory and use of these techniques was restricted

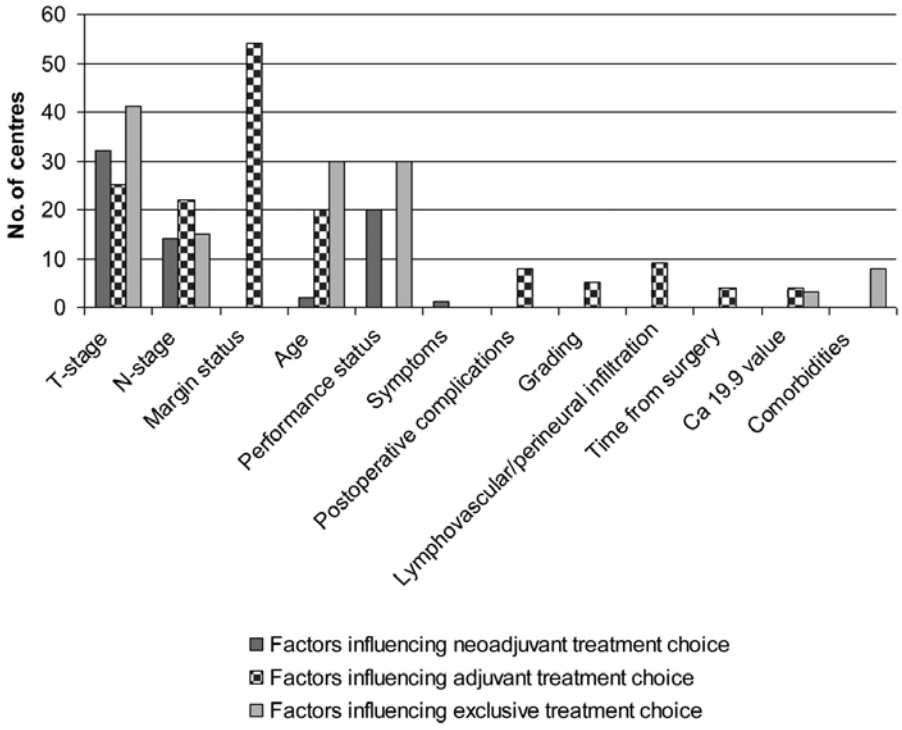

Figure 4. Factors influencing neoadjuvant (grey bar), adjuvant (black and white bar) and exclusive (pale grey bar) treatment.

to selected cases. Chest X-rays and biological markers for examination of polymorphism were not deemed necessary by 79 and 94% of responding centres, respectively. For the PC treatment, the majority of the physicians (63%) needed histological confirmation, although were prompt to perform the treatment only on clinical diagnosis (imaging-markers-symptoms) after a single (63%) or at least two (54%) biopsy attempts.

Session 3. This session investigated the core of RO approaches in terms of indication criteria, dose, fractionation and chemotherapy schedules. For convenience, this section was divided into three parts while taking into account the three potential approaches (neoadjuvant, adjuvant, exclusive and/or palliative) to the PC from the point of view of the radiooncologist. Clinical factors influencing the treatment approach for the three different settings (neoadjuvant, adjuvant and exclusive) are detailed in Fig. 4.

i) Neoadjuvant setting. This setting account for neoadjuvant RT (nRT), neoadjuvant chemoradiation (nCT/RT) and induction chemotherapy (iCT).

Thirty-eight percent of centres commonly stated the use of nCT/RT, while only 7.5% in selected cases. Clinical factors influencing the neoadjuvant choice are shown in Fig. 4. PC plus nodal drainage were the contoured target volumes and 45-55 Gy was the range of prescribed doses. Only eight RO services commonly used >50 Gy as a total dose. Mostly, fractionation was conventional with 1.8 and 2 Gy in 70 and 22%, respectively. The drugs used for radiosensitizing were gemcitabine (63.4%), 5-fluorouracil/capecitabine (26.8%) and others (9.8%).

Induction chemotherapy was performed routinely in 38.7% of cases and again 7.5% RT units selected iCT in certain cases. Results of the questionnaire suggested it was possible to indicate >1 iCT schedule per centre. The schedules most frequently used were gemcitabine-oxaliplatin (45%), gemcitabine alone (32.5%) or 5-fluorouracil-irinotecan-oxaliplatin (i.e., folfirinox) (12.5%) mostly with 3 or 4 cycles prior to RT (range, 1-12).

The specialist prescribing and administering chemotherapy drugs was the medical oncologist in 71% of cases and the radiation oncologist in the remaining 29%.

During a period of 2-8 weeks from the completion of neoadjuvant treatment about two third of centres (62.5%) performed clinical instrumental restaging (Fig. 3), mostly after 4 or 6 weeks.

ii) Adjuvant setting. This setting accounted for adjuvant RT (aRT) followed by chemotherapy, adjuvant chemoradiation (aCT/RT) and adjuvant chemotherapy (aCT).

Sixty-two percent of centres declared the use of aCT-RT or aRT followed or not by chemotherapy. The aRT was prescribed to PC bed at doses ranging from 45 to 54 Gy in 91% of cases. Doses >50 Gy were applied in 19 centres. Nodal drainage in the same dose range was irradiated by 97% of responders. Almost always conventional fractionation was applied. The drugs most frequently used for radiosensitizing were gemcitabine (58%) or 5-fluorouracil/capecitabine (i.v. or per os) (40%), although (2%) a two-drug schedule (gemcitabine plus oxaliplatin) was rarely used. After aRT, 2-4 chemotherapy cycles were added and administered by the majority of centres.

Adjuvant CT was the treatment declared by 47 (58.7%) of the centres, while 15% of responders stated use of this technique in selected cases and 26% of RT units did not perform it in order not to compromise concomitant chemoradiation treatment or due to patient performance status or the decision of the medical oncologist.

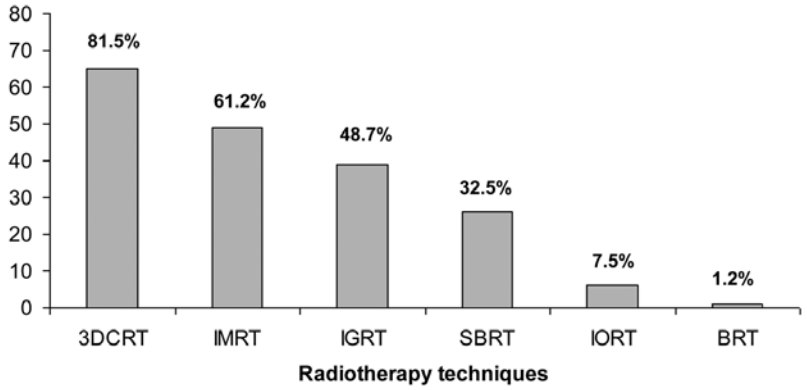

Figure 5. Number of centres using the reported radiotherapy techniques.

The most frequently used drugs were gemcitabine alone (58.6%), gemcitabine-oxaliplatin (20.7%) or 5-fluorouracil/capecitabine (13.8%) with a number of scheduled cycles ranging from 1 and 10 before RT, although 2, 3 or 6 cycles were the most performed.

Again, the specialist prescribing and administering concomitant chemotherapy was the medical oncologist in 74% of cases and the radiation oncologist in the remaining 18%. A minority of centres (8%) did not reply to this question. In the period between 8 and 12 weeks from adjuvant treatment completion, 65% of centres performed first follow-up (Fig. 3).

iii) Exclusive and palliative setting. This section account for exclusive radiation or chemoradiation (eCT/RT), exclusive chemotherapy (eCT), and palliative radiotherapy (pRT) for the treatment of locally advanced PC unfit for surgery.

Forty-six (57.5%) and 10 (12.5%) of centres used eCT/RT always or in selected cases, respectively. The dose prescribed to PC ranged between 24 and 66 Gy in 10-34 fractions, and 57 RO units performed nodal irradiation. The drugs most frequently used as radio sensitizing were gemcitabine alone (56.3%) or 5-fluorouracil/capecitabine (41.8%).

Forty-five (56.25%) and 8 (10%) of RO units declared the use of eCT in unresectable patients always or in selected cases, respectively. The schemes most frequently used were gemcitabine-oxaliplatin (44.2%), gemcitabine alone (36.5%), folfirinox (13.5%) or 5-fluorouracil/capecitabine (5.8%) with a number of scheduled cycles ranging from 2 to 12, although 3, 4 or 6 were the more frequent numbers of cycles administered.

Forty percent of investigated centres declared the use of pRT, being treated either loco-regional disease (tumour and/or lymph nodes) as well metastases.

Session 4. Treatment techniques for PC irradiation available at censored centres are reported in Fig. 5. The vast majority (81.5%) had the possibility to use a 3D-conformal radiotherapy technique. Intensity-modulated radiotherapy and image-guided radiotherapy were available in 61.2 and 48.7% of cases, respectively. SBRT was an emerging technique and was applied in 32.5% of RO units.

Immobilization systems were used in 84% of centres, while a set-up CT scan with intravenous contrast medium was used (always or in selected cases) in 44% of cases against 56% not employing it. Six RO units stated the routine use of gating systems against 55 that did not use it, while 15 RO services used gating when the clinical situation required it specifically. Forty-four centres performed routine image fusion in the treatment planning process, while 23 only when the clinical situation specifically required it.

As regards the last question: 'Your centre may be willing to participate in a national study on treatment of PC', most clinicians answered 'yes, of course' (97%), while a small number (3%) refused.

Discussion

To the best of our knowledge, few studies on PC patterns of RT practice are available (4-7) worldwide and no information is available regarding the Italian reality.

In the present survey, we have focused on the Italian PC radiotherapy practice in 2012, collecting data from 80 (57%) RO units distributed throughout the country. In comparison with other RO surveys conducted in Italy in 2012 (lung cancer) and 2008 (breast and head/neck cancer), the number of responding centres was encouraging, being 45, 48 and 50%, as reported by Ramella *et al* (8), Aristei *et al* (9) and Frata *et al* (10), respectively. This finding reveals an increased sense of membership of radiation oncologists in the RO community and a willingness to deepen their knowledge of the Italian reality in order to improve the quality of their investigation.

The survey attempted to address important issues such as: the main causes of non-indication to radiation treatment, the actual number of patients treated by Italian RO, the preferred or 'mostly chosen' treatment setting and the most applied RT techniques.

Concerning the main causes of non-indication to radiation treatment, our results indicated that slightly less than half of the patients (45%) were referred to RT services in poor general condition or carrying severe co-morbidities. This finding should be compared to previous intensive systemic treatments that heavily impacted on patient performance status, and is a bit discordant with the fact that 63% of the centres participating in the survey reported a tumour board with periodic meeting.

A second cause was the perception of lack of guidelines that was impacted by 25% of the non-indication to radiation treatment. In fact, the clinical target volume contouring proposal in preoperative/definitive and postoperative PC settings was suggested (11,12). Moreover, AIRO-GI groups published a handy, pocket-sized manual that summarizes the

main gastrointestinal guidelines [(13) available on line at www.radioterapiaitalia.it/Linee guida AIRO)]. It is likely, however, that the time between these publications and the administration of the survey was not sufficient for their spreading and validation.

The absolute figure of PC patients (N=568) treated by RO services in 2012 was low when compared with 11,400 PC esteemed cases in 2012 (14). However, it is to be considered that ~40% of patients exhibited metastatic disease at diagnosis and underwent chemotherapy or best supportive care. Moreover, a potential bias may lie in the fact that only 57% of the 140 Italian centres replied to the questionnaire, and of these, only 69% of centres declared the absolute number of irradiated patients. This figure reflects the changing scenario of international guidelines and the results of randomized trials that have raised questions regarding the optimal treatment of PC. Nevertheless, radiation oncologists have considerable room for improvement in terms of treatment strategies and patterns of RT as well as in terms of combined efforts in prospective studies investigating new combinations of chemotherapy and/or biologic agents with RT.

The present study also showed the current treatment of patients with PC in Italian hospitals. In a previously conducted meta-analysis the efficacy of neoadjuvant chemoradiation in patients with PC was investigated (15). The authors of that meta-analysis concluded that for patients with resectable tumours, the current data did not suggest an obvious advantage of neoadjuvant therapy. By contrast, patients presenting locally advanced/unresectable tumours were offered neoadjuvant therapy and then re-evaluated for resection (15). In the Japanese survey, there was no mention of a neoadjuvant approach, although authors reported that 20.8% of patients were treated using an investigational protocol (6). Our data showed that ~38% of centres reported the use of nCT/RT or nCT approach. These data are also higher than the German ones. Boeck *et al* reported a 21% proportion of neoadjuvant treatment considering the latter unjustified, outside of clinical trials, due to the lack of evidence based rationale for this therapy (4). The discrepancy with international data may be owing to different national guidelines: in Italy, AIOM guidelines suggest that the evaluation of neoadjuvant approach for borderline resectable PC patients (16) should be performed by a tumour board. A second explanation for the relatively high percentage of neoadjuvant treatments is selection bias. PC observed by RO was pre-selected by surgeons and clinical oncologists as potential candidates to irradiation, and this upstream selection justified the high rate of nCT/RT subsequently performed. Furthermore, an incorrect understanding of the so-called term 'neoadjuvant treatment' including operable patients, border-line resectable and locally advanced PC was considered a third possible explanation.

Evidence suggests gemcitabine-oxaliplatin followed by gemcitabine alone were the most employed nCT schedules, administered mostly by 3-4 scheduled cycles (range, 1-12) prior to RT (15). The drug most used for radiosensitizing was gemcitabine (63.4%), followed by 5-fluorouracil/capecitabine (26.8%). Andriulli *et al* (17) assessed the benefit of neoadjuvant/preoperative gemcitabine chemotherapy used alone or in combination with other agents and/or concurrent radiotherapy in patients with localised PC. The results from that meta-analysis provided marginal support regarding the benefits of neoadjuvant/preoperative gemcitabine chemotherapy for patients with localised PC, but indicated a potential advantage for only a minority of those with unresectable lesions. Gemcitabine-based neoadjuvant/preoperative therapies showed a promising rate of tumour response, although at the expense of considerable toxicity (17).

No definite standard has been established in the adjuvant treatment of PC. The available data from randomized phase III trials (ESPAC-1 and CONKO-001) indicate that adjuvant chemotherapy may substantially prolong DFS and cause a moderate increase of overall survival (18-21). However, an optimal chemotherapy regimen remains to be defined. Notably, in Italy as well as in Germany (4), gemcitabine chemotherapy [according to the CONKO-001 trial (20,21)] was the preferred schema, while aCT according to the 'Mayo regimen' [bolus 5-FU plus folinic acid, ESPAC-1 study (19)] was selected by few physicians. A reduction in toxicity was cited as the explanation, based on the ESPAC-3 trial, whereas gemcitabine was not superior to the Mayo regimen with respect to the primary end-point of overall survival, although the authors reported a 50% reduction of treatment-associated serious adverse events using gemcitabine (22). In our survey approximately two third of centres reported the use of aCT/RT or aCT approach, with a slight predominance of aCT/RT that again could be explained, considering that centres that adhere to the survey are potentially the most active in the research field and/or the aforementioned upstream patient selection.

Although the optimal RT dose has yet to be defined, the NCCN guidelines have recommended a dose of 50-60 Gy and of 45-54 Gy at conventional fractionation for primary definitive chemoradiation and postoperative RT, respectively (23). Moreover, large outcomes-based analysis for patients treated with adjuvant radiotherapy in resected PC showed that the optimal dose appears to decrease between 50 and 55 Gy and patients treated within this range had the longest median overall survival (24). In the present survey, most patients were treated with a total dose of 50-54.9 Gy in the exclusive and postoperative groups. Major deviations from these doses were probably associated with the SBRT technique used in 26 centres. Therefore, Italian radiation oncology centres as well as the Japanese ones (6) appear to have appropriatedly utilized the literature guideline recommendations. Of note, no dose data have been reported by German authors (4).

Concerning the RT volumes, in the majority of patients, the primary neoplasm (or tumour bed) plus local drainage were irradiated, irrespective of the treatment setting. Although there is no consensus concerning the elective nodal irradiation (ENI) in PC, it may be justified in a treatment with curative intent due to the high frequency of lymphatic spread (60-80%) reported in head PC (25-27) and the high rate of local and nodal failure (up to 75%) (28,29). Therefore, NCCN practice guidelines have recommended that when 5-FU-based chemoradiotherapy is used, the treatment volumes should include the primary tumour location and the regional lymph nodes (23). Previous reports have indicated that the rate of severe toxicity is greater in patients treated with gemcitabine-based chemoradiotherapy than in those treated with 5-FU-based chemoradiotherapy (17,30). Additional studies investigating the optimal radiation field when using chemotherapy drugs, such as gemcitabine, should be conducted. In particular,

it is essential in the Italian scenario whereas the drug most frequently used for radiosensitizing was gemcitabine alone (58%) or in combination with oxaliplatin (2%).

With regard to the RT treatment technique, computed tomography-based treatment planning and 3DCRT were used for >80% of patients, respectively. This finding is in accordance with the NCCN guidelines (23) and reveal an high quality level of RO procedures.

Moreover, 61% of PC may be treated by IMRT and 49% by IGRT. These percentages are noteworthy and suggest that probably PC patients are more likely to be irradiated in technology-advanced structures as compared to less equipped hospitals. Notably, SBRT with or without 3DCRT was frequently reported in Italy. A growing body of literature has contributed to the spread of this latter technique (31-34), which can improve local control by increasing doses without impairing normal tissue. Additional prospective studies are required to assess the efficacy of SBRT in PC.

A main drawback of the present study was the number of responding centres that, although higher than in previous surveys (8-10), limited the analysis. Moreover, we cannot deny heterogeneity in our analysis due to different interpretations of survey queries.

In conclusion, the present study has shown that extensive variation exists with regard to treatment strategies and the patterns of RT. Nevertheless, a favourable attitude towards cooperative studies emerged from the national survey that provided evidence for improved PC treatment in Italy. In the future, repeated surveys and point-by-point comparisons with the results from other countries may demonstrate how RO for PC has been developed and optimized in adhering to the international standard of care.

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