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Radiotherapy as treatment option in biliary cancer patients: a national survey of AIRO (Italian Association of Radiation Oncology) Gastroenterology Group

Valentina Lancellotta[1], Mattia Falchetti Osti[2], Giancarlo Mattiucci[1], Alessio Morganti[3], Vittorio Bini[4], Cynthia Aristei[5], Marco Lupattelli[6]

[1]Radiation Oncology Department, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy
[2]Department of Radiation Oncology, Sant'Andrea Hospital, Rome, Italy
[3]Radiation Oncology Unit, Department of Experimental, Diagnostic and Specialty Medicine, DIMES, University, S. Orsola-Malpighi Hospital, Bologna, Italy
[4]Internal Medicine, Endocrine and Metabolic Science Section, University of Perugia, Italy
[5]Radiation Oncology Section, Department of Surgical and Biomedical Sciences, University and General Hospital, Perugia, Italy
[6]Radiation Oncology Section, General Hospital, Perugia, Italy

ABSTRACT

Background: The aim is to find out how many radiation oncology centres treat biliary duct carcinoma (BDC), what treatments they offer and whether they would be interested in developing prospective trials.

Materials and methods: A questionnaire was posted to all 220 Italian Radiation Oncology Centres. The survey consisted of 31 eligibility questions in a combination of multiple and forced choice formats addressing the following parameters: characteristics of the centre, numbers of BDC patients treated, treatment options, radiotherapy parameters (target definition, schedule, technique, dose constraints) and interest in developing future randomized trials.

Results: No major differences emerged in BDC management, whatever the site, and whether it was resectable or not. Discrepancies in routine clinical practice were, however, observed with lack of agreement on expansion margins, dose constraints and treatment schedules for the stereotactic technique and palliative treatments.

Conclusions: The present survey attempted to fill the gaps in the role of radiotherapy in patients with BDC. Since lack of prospective randomized studies and disease rarity have mitigated against an evidence-based approach, patients with BDC should be enrolled in prospective studies. The above-mentioned results should also emphasize the need to combine analysis of treatment results from all Italian centres in order to create predictive models.

Key words: abdomen irradiation; chemoradiotherapy; brachytherapy

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Introduction

Biliary duct carcinoma (BDC) accounts for at least 3–4% of all gastrointestinal tumours; it is associated with poor prognosis as < 20% of patients are suitable candidates for surgery which is the only effective treatment [1, 2]. Prognosis depends in part on the anatomic location of the tumour, which affects its resectability. Total resection is higher for distal biliary duct lesions than for proximal ones. However the rate of relapse is as high as 60–75%, even if clear resection (R0 resection) is possible [3]

Address for correspondence: Marco Lupattelli, Radiation Oncology Section, General Hospital, Perugia, Italy; e-mail: mlupattelli62@gmail.com

In patients with locally advanced disease (mainly status N+ or R1–R2), postoperative external beam radiotherapy (EBRT) plus chemotherapy may improve local control and overall survival [4–6]. In unresectable disease, EBRT (plus intra-luminal brachytherapy (BRT) in the extrahepatic cholangiocarcinoma) with or without chemotherapy may affect clinical outcomes [7, 8]. In the palliative setting, the addition of BRT to the biliary stent position reduces the tumour growth and prolongs biliary patency. The safe and effective combination of biliary stent and BRT may improve quality of life [9–11].

Recently, preliminary studies related to stereotactic body radiotherapy in both intrahepatic and extrahepatic disease have documented an acceptable toxicity profile and local control with a dose-response relationship [12, 13].

Despite these data, the role of radiotherapy in biliary carcinoma remains under debate. Little or no scientific evidence is available in favour of one approach or another because prospective randomized trials are lacking due to disease rarity. Recommendations from national [14, 15] and international guide-lines [16, 17] are mainly based on retrospective studies, systematic reviews or, more often, indications for radiotherapy are discussed in multi-disciplinary groups, with choice of treatment at the physicians' discretion [14, 18, 19].

Within the Italian Association of Radiation Oncology, the Gastroenterology Group conducted a nationwide questionnaire-based survey on BDC, with the aims of finding out how many radiation oncology centres treat BDC, what treatments they offer and whether they would be interested in developing future randomized trials.

Materials and methods

In June 2015, a questionnaire was posted to all 220 Italian Radiation Oncology Centres. Practising radiation oncologists were asked to fill it in and return it by post, fax or email before December 2015. No fee or incentive was offered; participation was voluntary and anonymous. To encourage participation, AIRO co-ordinated two follow-up e-mails to all participants within 1 month of the initial e-mailing. The survey consisted of 31 eligibility questions in a combination of multiple and forced choice formats addressing the following parameters: characteristics of the centre (questions 1–6), numbers of BDC patients seen, treated, followed-up with radiation therapy per year (questions 7–10), therapy for the intra-hepatic and extra-hepatic biliary tracts and the gallbladder (questions 11–13), target definition and treatment schedule (questions 14–18), radiotherapy technique and dose constraints (questions 19 and 20), brachytherapy (questions 21–31) and interest in developing future randomized trials (32) (Fig. 1). For the statistical analysis data are shown as frequencies.

General data

1) Radiotherapy Center (indicate: 1 = public; 2 = private; 3 = private agreement; 4 = university):

2) Do patients with biliary tract neoplasia come to your Institution? (Yes / No):

3) Is there a multidisciplinary work group in your health facility for the treatment of patients with biliary tract neoplasia (Yes/No)?

4) Group members (Yes/No):
Pathologist _____
Surgeon _____
Gastroenterologist _____
Medical Oncologist _____
Radioterapist _____
Radiologist _____
Interventional radiologist _____
Other members (specify) _____

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

5) Indicates the main reasons if the figure of the radiotherapist was not included in the list of participants in the multidisciplinary group or the radiotherapy treatment was not considered a therapeutic option that can be proposed at your Center (more answers possible, indicate the 3 most frequent reasons, numbering them progressively from 1 [most important] to 3 [least important]):

- failure to indicate in national or international guidelines: |__|
- internal guidelines: |__|
- lack of dedicated radiotherapist |__|
- lack of suitable technology for the treatment of this tumor: |__|
- lack of experience in the treatment of that tumor: |__|
- other (specify) _____

6) Do patients suffering from biliary tract neoplasia come to your Radiotherapy Unit for evaluation regardless of the existence of a multidisciplinary group and the participation of the radiotherapist oncologist to the work group (Yes/No)? (e.g. patients referred by a single specialist — medical oncologist, surgeon - or symptomatic patients for palliative treatment)

Yes: |__| NO: |__|

Radiotherapy treatment

(to be filled in only if radiotherapy treatments for biliary tract neoplasms are performed in your Center)

7) Indicates the start year of radiotherapy treatments and the total number of patients treated at your Center.

Treatment start year |_____|

Total number of patients treated since this date < 5 |__| 5–10 |__| > 10 |__| > 20 |__| > 30 |__| > 50 |__|

Among the patients treated, how many affected by intrahepatic biliary tract neoplasia? _____

8) Indicates the number of patients treated with radiotherapy at your Center in the last year (2014)

No. of patients treated in the last year <5 |__| > 5 ≤ 10 |__| > 10 |__|

9) Are the patients treated at your Center part of national mono-institutional or cooperative study projects? If YES, what percentage?

NO: |__| Yes: |__| Percentage _____

10) Indicate the intent with which they are treated at your Center

- Radical/adjuvant intent |__|
- Palliative intent |__|
- Both radical/adjuvant and palliative intent (depending on the clinical case) |__|

11) What kind of treatment do you perform at your Center in resectable disease?

Intrahepatic biliary disease

- If R0 and LN uninvolved (N0), follow-up |__|
- Postoperative radiotherapy if (multiple responses possible):

— R1 |__|

— R2 |__|

— N + |__|

— Never |__|

— Other _____

Post-operative chemotherapy:

— Exclusive |__|

— Sequential and concomitant RT |__|

— Concomitant |__|If so, when and which scheme?_____

Extrahepatic biliary disease.

- If R0 and LN uninvolved (N0), follow-up |__|
- Postoperative radiotherapy if (multiple responses possible):

— R1 |__|

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

— R2 |__|
— N + |__|
— Never |__|
— Other _____
Post-operative chemotherapy:
— Exclusive |__|
— Sequential and concomitant RT |__|
— Concomitant |__|
If so, when and which scheme? _____

Gallbladder

- If R0 and LN uninvolved (N0), follow-up |__|
- Postoperative radiotherapy if (multiple responses possible):

— R1 |__|
— R2 |__|
— N + |__|
— Never |__|
— Other _____
Post-operative chemotherapy:
— Exclusive |__|
— Sequential and concomitant RT |__|
— Concomitant |__|
If so, when and which scheme? _____

12) What kind of treatment do you perform at your Center in unresectable disease?
Intrahepatic biliary disease
Radiotherapy (multiple responses possible):
— Exclusive |__|
— Never |__|
— Other _____

Chemotherapy:
— Exclusive |__|
— Sequential and concomitant RT |__|
— Concomitant |__|
If so, when and which scheme? _____

Extrahepatic biliary disease
Radiotherapy (multiple responses possible) based on the clinical context:
— RT exclusive |__|
— RT + brachytherapy |__|
— Exclusive brachytherapy |__|
— Never |__|
— Other_____
Chemotherapy:
— Exclusive |__|
— Sequential and concomitant RT |__|
— Concomitant |__|
If so, when and which scheme? _____

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

Gallbladder.

Radiotherapy (multiple responses possible) based on the clinical context:

— RTE exclusive |__|

— Never |__|

— Other _____

Chemotherapy:

— Exclusive |__|

— Sequential and concomitant RT |__|

— Concomitant |__|

If so, when and which scheme? _____

13) What workflow is typically followed at your Center for the definition of RT volumes (indicate the standard procedure)?

- Performing diagnostic imaging (CT and/or RM contrast) in treatment position and fusion with simulation CT performed without contrast|__|
- Performing diagnostic imaging (CT and/or RM contrast) not in treatment position and fusion with simulation CT performed without contrast |__|
- Execution of simulation CT without contrast medium |__|
- Execution of 4D simulation CT without contrast medium |__|

RM use (rate) _____

14) Indicates the clinical volume of treatment (CTV) typically outlined at your Center

If SBRT

Intrahepatic biliary disease

GTV + margin ≤ 5 mm = CTV |__|

GTV + margin >5 ≤ 10 mm = CTV |__|

GTV=CTV |__|

Other (specify)_____

Extrahepatic biliary disease

GTV + margin ≤ 5 mm = CTV |__|

GTV + margin > 5 ≤ 10 mm = CTV |__|

GTV=CTV |__|

Other (specify)_____

Gallbladder

GTV + margin ≤ 5 mm = CTV |__|

GTV + margin >5 ≤ 10 mm = CTV |__|

GTV=CTV |__|

Other (specify)_____

If conventional fractionation

Intrahepatic biliary disease

Defined according to guidelines: NO |__| YES |__|; and if YES

— Institutional |__|

— National (define which) |__| _____

— International (define which ones) |__| _____

Defined based on the clinical context |__|

Other _____

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

Extrahepatic biliary disease
Defined according to guidelines: NO |__| YES |__|; and if YES
— Institutional |__|
— National (define which) |__| _____
— International (define which ones) |__| _____
Defined based on the clinical context |__|
Other _____

Gallbladder
Defined according to guidelines: NO |__| YES |__|; and if YES
— Institutional |__|
— National (define which) |__| _____
— International (define which ones) |__| _____
Defined based on the clinical context |__|
Other _____

15) Indicate the CTV-PTV margin (isotropic or anisotropic) typically adopted at your Center
Intrahepatic biliary disease
Conventional fractionation: margin mm _____
Hypofractionation: margin mm _____
Other (specify)_____

Extrahepatic biliary disease
Conventional fractionation: margin mm _____
Hypofractionation: margin mm _____
Other (specify)_____

Gallbladder
Conventional fractionation: margin mm _____
Hypofractionation: margin mm _____
Other (specify)_____

16) Indicate the type of fractionation typically adopted at your Center
Intrahepatic biliary disease
Conventional fractionation |__|
Hypofractionation (SBRT) |__|
SIB |__|
Other (specify)_____

Extrahepatic biliary disease
Conventional fractionation |__|
Hypofractionation (SBRT) |__|
SIB |__|
Other (specify)_____

Gallbladder
Conventional fractionation |__|
Hypofractionation (SBRT) |__|
SIB |__|
Other (specify)_____

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

17) Indicates the total prescription dose and fractionation typically used at your Center for a radical or adjuvant intent treatment (initialed respectively with capital letter R or A)

Intrahepatic biliary disease (conventional fractionation).

Total dose 50–54 Gy |__| |__|
Total dose > 54 Gy ≤ 60 Gy |__| |__|
Total dose > 60 Gy |__| |__|
Any comments

Extrahepatic biliary disease (conventional fractionation).

Total dose 50–54 Gy |__| |__|
Total dose > 54 Gy ≤ 60 Gy |__| |__|
Total dose > 60 Gy |__| |__|
Any comments

Gallbladder(conventional fractionation).

Total dose 50–54 Gy |__| |__|
Total dose > 54 Gy ≤ 60 Gy |__| |__|
Total dose > 60 Gy |__| |__|
Any comments

Intrahepatic biliary disease (SBRT). (indicate the most frequently adopted RT schedules)

Fraction's number |__| Dose per fraction |__|
Fraction's number |__| Dose per fraction |__|
Fraction's number |__| Dose per fraction |__|
Any comments _____

Extrahepatic biliary disease (SBRT). (indicate the most frequently adopted RT schedules)

Fraction's number |__| Dose per fraction |__|
Fraction's number |__| Dose per fraction |__|
Fraction's number |__| Dose per fraction |__|
Any comments _____

Gallbladder (SBRT). (indicate the most frequently adopted RT schedules)

Fraction's number |__| Dose per fraction |__|
Fraction's number |__| Dose per fraction |__|
Fraction's number |__| Dose per fraction |__|
Any comments _____

18) Indicates total dose and fractionation typically adopted at your Center for purely symptomatic treatment (palliation)

Intrahepatic biliary disease Fraction's number |__| Dose per fraction |__|
Extrahepatic biliary disease Fraction's number |__| Dose per fraction |__|
Gallbladder Fraction's number |__| Dose per fraction |__|

19) Indicate the treatment technique typically adopted at your Center (more answers possible, indicate with 1 and 2 the techniques most frequently adopted)

Intrahepatic biliary disease

Static 3D technique with multiple coplanar or non-coplanar beams |__|
Kinetic 3D technique with multiple coplanar or non-coplanar beams |__|
Intensity Modulated (static, volumetric) with coplanar or non-coplanar beams / arcs |__|
Tomotherapy |__|
Robotic technique (Cyber-knife) |__|
Other (specify) _____

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

Extrahepatic biliary disease
Static 3D technique with multiple coplanar or non-coplanar beams |__|
Kinetic 3D technique with multiple coplanar or non-coplanar beams |__|
Intensity Modulated (static, volumetric) with coplanar or non-coplanar beams / arcs |__|
Tomotherapy |__|
Robotic technique (Cyber-knife) |__|
Other (specify) _____

Gallbladder
Static 3D technique with multiple coplanar or non-coplanar beams |__|
Kinetic 3D technique with multiple coplanar or non-coplanar beams |__|
Intensity Modulated (static, volumetric) with coplanar or non-coplanar beams / arcs |__|
Tomotherapy |__|
Robotic technique (Cyber-knife) |__|
Other (specify) _____

20) Indicate the dose limits for OAR adopted at your Center
Liver |_____|
Kidney |_____| (or if diversified right kidney |_____| left kidney |_____|)
Small bowel |_____|
Spinal cord |_____|
Stomach |_____|
Duodenum |_____|
Jejunum |_____|
Other(specify)_____

Brachytherapy
21) Do you use BT in your Center for the treatment of extrahepatic biliary tract?
YES |__| NO |__| If YES, HDR |__| o LDR |__|
22) How many patients have you treated (indicate the period)?
_____
23) When do you use BT (multiple responses possible)?
Palliation |__|
Exclusive |__|
As a boost after ERT |__|

24) BT treatment mode: ERCP or PTC ?_____

25) Do you use prosthesis?:
NO |__| YES |__|
Type of prosthesis _____
Prosthesis positioning timing with respect to BT: _____

26) Planning: 2D _____ 3D _____ (specify%)

27) Treatment volumes and dose prescription:
GTV with 1-2cm cranio-caudal margin |__|; GTV with cranio-caudal margin less than 1cm |__|
Prescription at 1cm from the source |__|; Prescription <1cm from the source
Other _____

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

28) How many patients treated with:
- exclusive palliative intent _____
- radical intent (in association with ERT) _____

29) Dose and fractionation used:
Palliation _____
In association with ERT _____

30) After treatment, does the patient undergo a follow-up program?
YES |__| NO |__|

31) If yes, what kind?
Not intensive |__|
Intensive |__|
Specify type of exams for each type of follow-up performed _____
___

32) Would you be interested in participating in both retrospective (pooled analysis) and prospective study projects?
YES |__| NO |__|
Comments _____

Figure 1. A questionnaire was posted to Italian Radiation Oncology Centres

Results

In total, 36/220 (16%) centres responded to the questionnaire. Responders were distributed similarly in northern and central Italy (15 (41.6%) and 19 (52.7%), respectively) but only 2 (5.7%) responded from the south of Italy. The number of patients with BDC who were treated per year ranged from < 5 patients in 23 (63.8%) centres, ≤ 10 patients in 4 (11.1%) and > 10 patients in 1 (2.7%). Intention to treat in 75% centres was both palliative and adjuvant/radical.

For resectable disease, adjuvant radiotherapy was recommended when margins and lymph-nodes were positive by 22 responders (61%) for intra-hepatic disease, by 28 centres (77.7%) for extra-hepatic disease, and by 25 centres (69.4%) for gallbladder disease. Chemotherapy in combination with radiotherapy was the most common choice (52.7% intra-hepatic disease, 63.8% extra-hepatic disease and 50% gallbladder). Figure 2 shows treatment modalities for each BDC subtype.

For inoperable disease, exclusive radiotherapy was considered by 12 centres (33.3%) for intra-hepatic disease and by 14 centres (38.8%) for gallbladder disease. Chemotherapy alone was chosen by 9 centres (25%) for intra-hepatic disease and by 8 centres (22.2%) for gallbladder. Concomitant and sequential chemotherapy was recommended by 15 centres (41.6%) in intra-hepatic disease and by 14 centres (38.8%) for gallbladder. Six centres (16.6%) used concomitant chemotherapy for intra-hepatic disease and 5 centres (13.8%) for gallbladder.

For inoperable extra-hepatic disease, 17 centres (47.2%) considered only external beam radiotherapy (EBRT), 5 (13.8%) provided EBRT combined with BRT, 3 offered (8.3%) BRT alone and 2 (5.5%) did not prescribe radiotherapy.

Fluoropyrimidine (capecitabine, 5-fluorouracile), gemcitabine and cisplatin in monotherapy or in combination with each other were the most common chemotherapy agents for all disease sites, independently of disease stage.

Three dimensional conformal techniques (3D-CRT), stereotactic radiotherapy, and intensity modulated radiotherapy (IMRT) were the most common EBRT techniques used whatever the site. Figure 3 illustrates distribution of radiotherapy techniques.

Conventional fractionation was the most common schedule used (58.3% of centres for intra-hepatic, 75% of centres for extra-hepatic disease and 66.6% of centres for gallbladder). Figure 4 reports radiotherapy schedules. Both in the adjuvant setting and locally advanced unresectable disease, there was an agreement between

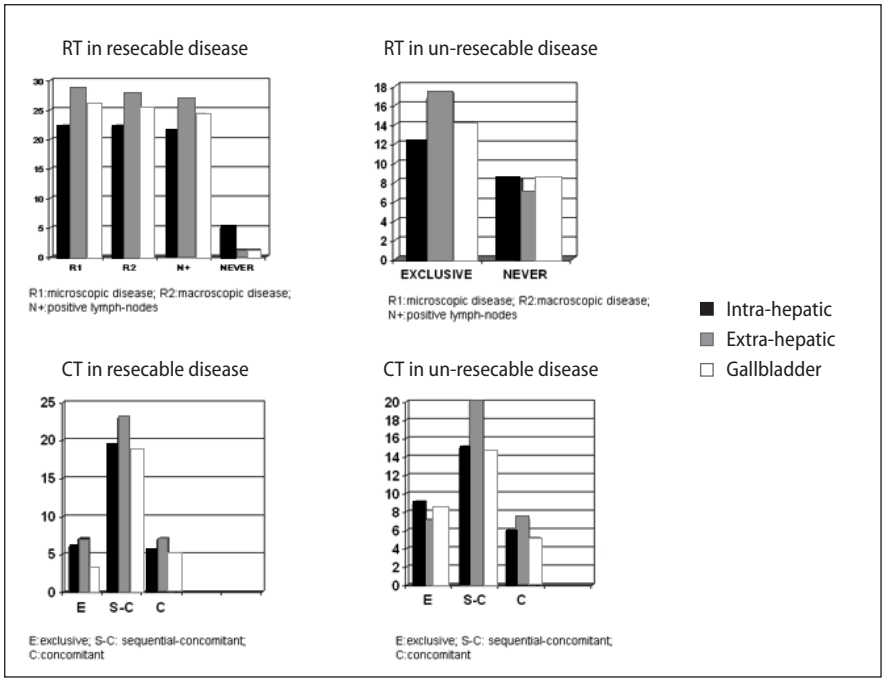

Figure 2. Choice of treatment modality by biliary duct carcinoma subtypes. RT — radiotherapy; CT — chemotherapy

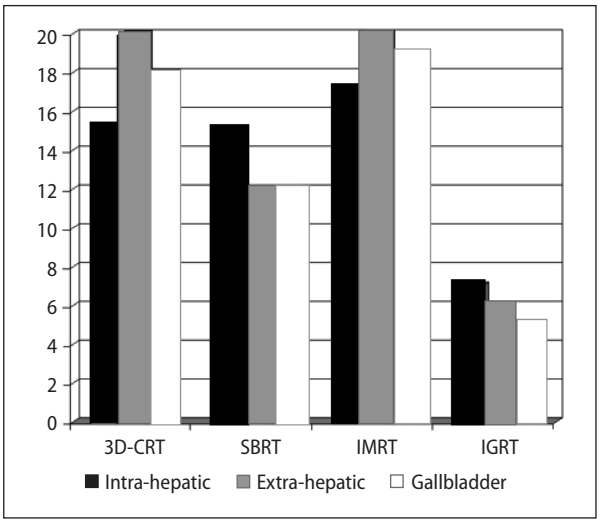

Figure 3. Radiotherapy technique. 3D-CRT — three dimensional conformal radiotherapy; SBRT — stereotactic radiotherapy; IMRT — intensity modulated radiotherapy; IGRT — image guided radiotherapy

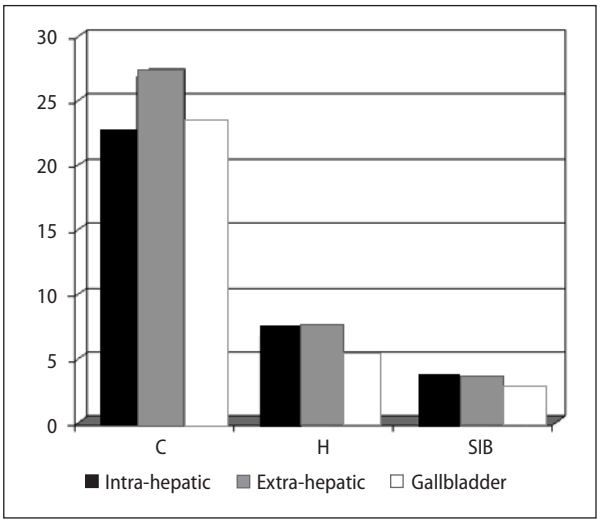

Figure 4. Schedule treatment. C —conventional; H — hypofractionated; SIB — simultaneous integrated boost

the responding centres to the survey as a total dose of 50–54 Gy and 54–60Gy, respectively, was recommended (Fig. 5).

There was no agreement on expansion, dose constraints and treatment schedules for stereotactic radiotherapy or palliative treatment.

Appropriate Italian national and international guidelines were followed by 21 centres (58.3%) for intra-hepatic disease, by 25 centres (69.4%) for extra-hepatic disease and by 24 centres (66.6%) for gallbladder. Figure 6 lists the most popular guidelines.

Only 5 centres (13.8%) performed BRT; but all agreed on intention to treat, treatment planning, doses and stent use. Most centres (69.4%) were interested in developing future prospective randomized trials.

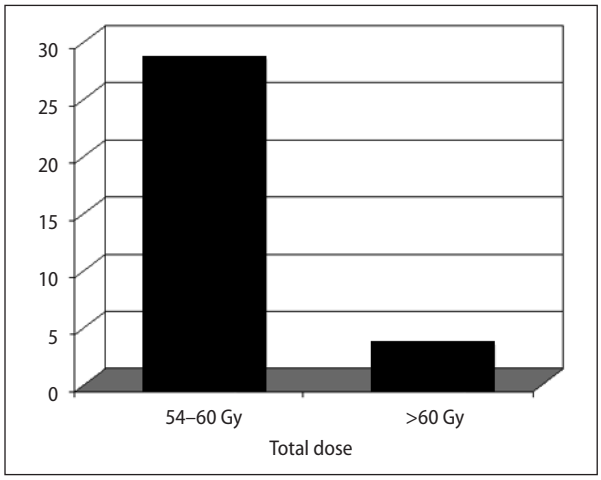

Figure 5. Total dose delivered in advanced disease. Gy — gray

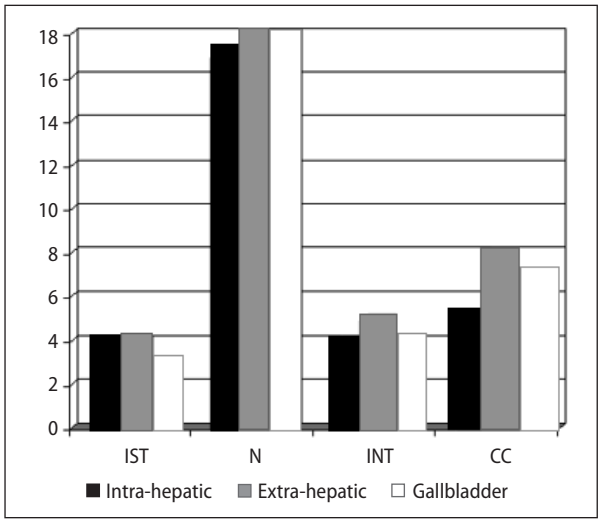

Figure 6. Use of Guidelines. IST — institutional; N — national; INT — international; CC — clinical context

Discussion

To our knowledge, this is the first survey about radiation oncology approaches to BDC. As usual, caution needs to be exerted when interpreting results from any questionnaire because they provide an image of reality that sometimes does not coincide with clinical practise as a result of the personal behaviour of the radiation oncologist responding to the survey. Nevertheless, on the whole, no major differences emerged in BDC management, whatever the site, and whether it was resectable or not. Good agreement may be due to the Gastrointestinal Italian Guidelines [14] that supported decision-making even in the absence of randomized trials.

Discrepancies in routine clinical practice were, however, observed with lack of agreement on expansion margins, dose constraints and treatment schedules for the stereotactic technique and palliative treatments. Unfortunately, survey responses precluded drawing any conclusions about the underlying reasons for these differences but they do suggest that future clinical trials should focus on providing evidence for optimizing and standardising BDC treatment.

Only 16% of Italian Radiation Oncology Centres responded to the questionnaire; this attitude may be related to the low incidence of the disease and lack of interest. Given the rarity of BDC, referring patients to specialised centres should perhaps be considered. In fact, 27/36 responding centres (75%) treated fewer than 10 patients/year and only 3 (3.3%) included patients in investigational protocols. These data are similar to those reported by a pattern of practice study on radiotherapy for BDC carried out by the Japanese Society of Radiotherapy Oncology [20].

Most radiation oncologists recommended adjuvant treatment in the subgroups of patients with pathologically positive nodes and/or microscopic residual disease (R1) as two meta-analysis showed a significantly lower mortality rate of patients treated with adjuvant radiotherapy than those treated with surgery alone [4–6, 21]. Unfortunately, no ongoing prospective study is analyzing the role of radiotherapy and one of the few randomized studies has been closed for poor accrual [22].

In the unresectable disease, the attitude of radiation oncologist was highly dependent on the anatomic location of the tumour; as radiotherapy alone or in combination with chemotherapy was recommended in only one third of intra-hepatic and gallbladder disease cases but in about two third of extra-hepatic tumours. These data may be related to the absence of efficacy arising from published studies and, therefore, to the awareness of therapeutic failure, even if recently in patients with intra-hepatic non-surgical tumour, the addition of radiotherapy to chemotherapy has significantly improved the overall survival [8].

The survey reveals a good agreement of radiation oncologists related to the adjuvant and radical treatment and the doses delivered, on the other hand. a poor agreement is documented in the set-

ting of stereotactic radiotherapy. In the few literature data, the feasibility and efficacy of this procedure is documented in terms of toxicity and local disease control. However, these studies were carried out on a limited number of cases, using different fractionations and total dose delivered; the probable dose-response correlation requires further investigation [12, 13, 23, 24].

First treatment schedule, whether for exclusive or adjuvant therapy, was, in 75% of Centres, a total dose of 50–54 Gy as delivered with EBRT. The same attitude was reported by the Japanese pattern of practice for BDC and guide-lines [20]. IMRT is the most used technique and this data is supported by the SWOG 8909 trial [25] which documents the feasibility and efficacy in terms of toxicity and outcomes in the adjuvant setting. Nevertheless, higher doses are limited by the tolerance of adjacent organs at risk, such as the liver, duodenum and stomach. In the unresectable extra-hepatic disease, BRT may overcome this limitation because it is associated with high radiation dose conformity within the target volume, rapid dose fall-off in adjacent organs at risk, relatively short treatment times and good functional outcomes. In patients with unresectable BDC, studies comparing EBRT plus BRT with EBRT alone showed better local control in the first group but no difference in the 2-year disease specific survival [9, 18, 19]. In patients with malignant biliary obstruction BRT played a major role in the palliative setting as stenting in combination with BRT provided a longer patency and survival [26–29]. Unfortunately, the present survey showed that only 5 Italian centres (13.8%) performed BRT, perhaps because of lack of experience and skill or current interest in modern EBRT equipment. However, the limited use of BRT was also documented in the Japanese pattern of practice [20].

Many centres recommended adjuvant chemotherapy in combination or not with radiotherapy. This attitude seems to be mainly based on two randomized trials and one meta-analysis [4, 30, 31] Recently, the results of two randomized phase III trials have been reported. The French trial (ACCORD 12-Prodige 18) comparing follow-up after surgery vs. adjuvant chemotherapy with gemcitabine-oxaliplatin did not show differences in terms of overall and disease-free survival [32]; while in the preliminary results of the BILCAP study adjuvant capecitabine obtained an improvement of clinical outcomes over postsurgical follow-up alone [33]. Not surprisingly, the most commonly used drugs for chemotherapy were fluoropyrimidine (capecitabine or 5-fluorouracil), gemcitabine and cisplatin in monotherapy or in combination. The phase III ABC-02 study showed that a combination of gemcitabine and cisplatin improved overall and progression-free survival by 30% over gemcitabine alone which may be considered the standard regimen in BDC [34]. Apart from the SWOG trial no prospective phase II or randomized trials using a combination of gemcitabine-capecitabine have been published.

The main limitation of the present investigation was the response rate to the survey. It appears low and is, indeed, lower than response rates elsewhere, [35] probably due to the rarity of BDC. Despite the fact that this survey provided a snapshot of attitudes towards BDC in Italian radiotherapy centres at that particular moment in time. It is to be hoped that these data will provide the basis for future clinical studies so as to ensure an evidence-based approach to BDC.

Conclusions

The present survey attempted to fill the gaps in the role of radiotherapy in patients with BDC. Since lack of prospective randomized studies and disease rarity have mitigated against an evidence-based approach, patients with BDC should be enrolled in prospective studies. We think the above-mentioned results should also emphasize the need to combine analysis of treatment results from all Italian centres in order to create predictive models [36].

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