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FULL PAPER

Intensity-modulated extended-field chemoradiation plus simultaneous integrated boost in the pre-operative treatment of locally advanced cervical cancer: a dose-escalation study

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Objective: To investigate the feasibility and determine the recommended pre-operative intensity-modulated radiotherapy (IMRT) dose of extended-field chemoradiation along with simultaneous integrated boost (SIB) dose escalation.
Methods: A radiation dose of 40 Gy over 4 weeks, 2 Gy/fraction, was delivered to the tumour and the lymphatic drainage (planning target volume, PTV3), which encompassed a volume larger than standard (common iliac lymphatic area up to its apex, in front of the L3 vertebra), concurrently with chemotherapy (cisplatin and 5-fluorouracil). Radiation dose was escalated to the pelvis (PTV2) and to the macroscopic disease (PTV1) with the SIB-IMRT strategy. Three dose levels were planned: Level 1 (PTV3: 40/2 Gy; PTV2: 40/2 Gy; PTV1: 45/2.25 Gy), Level 2 (PTV3: 40/2 Gy; PTV2: 45/2.25 Gy; PTV1: 45/2.25 Gy) and Level 3 (PTV3: 40/2 Gy; PTV2: 45/2.25 Gy; PTV1: 50/2.5 Gy). All treatments were delivered in 20 fractions. Patients were treated in cohorts of between three and six per group using a Phase I study design. The recommended dose was exceeded if two of the six patients in a cohort experienced dose-limiting toxicity within 3 months from treatment.
Results: 19 patients [median age: 46 years; The International Federation of Gynecology and Obstetrics (FIGO) stage IB2: 3, IIB: 10, IIIA–IIIB: 6] were enrolled. Median follow-up was 24 months (9–60 months). The most common grade 3/4 toxicity was gastrointestinal (GI) (diarrhoea, mucous discharge, rectal/abdominal pain). At Levels 1 and 2, only one grade 3 GI toxicity per level was recorded, whereas at Level 3, two grade 3 GI toxicities (diarrhoea, emesis and nausea) were recorded.
Conclusion: The SIB-IMRT technique was found to be feasible and safe at the recommended doses of 45 Gy to PTV1 and PTV2 and 40 Gy to PTV3 in the pre-operative treatment of patients with locally advanced cervical cancer. Unfortunately, this complex technique was unable to safely escalate dose beyond levels already achieved with three-dimensional conformal radiotherapy technique given acute GI toxicity.
Advances in knowledge: A Phase I radiotherapy dose-escalation trial with SIB-IMRT technique is proposed in cervical cancer. This complex technique is feasible and safe at the recommended doses.

INTRODUCTION

Even with the advent of exclusive chemoradiation [CT/radiotherapy (RT)] as the standard treatment for locally advanced cervical cancer (LACC) since 1999,[1] the 5-year overall survival (OS) still remains around 70% in this subset of patients. It is well known that radical surgery (RS) following CT/RT is not a worldwide standard strategy. Nevertheless, investigational approaches that use completion surgery after CT/RT or chemotherapy have also been investigated with the aim to remove potentially radioresistant and chemoresistant

tumour foci, evaluate pathological response and improve local control (LC) and possibly OS. Indeed, pre-operative CT/RT has been reported to achieve very encouraging results in terms of extent of LC and OS,[2–7] albeit concerns have been raised about the potential increase of the rate and the severity of treatment-related side effects.[8,9]

Results of the GYNECO 02 trial seemed to suggest that completion hysterectomy had no therapeutic impact in patients with clinical and radiological complete response after chemoradiation, although this conclusion was limited by the lack of power.[10] On the other hand, the Phase III study by Cetina et al[11] demonstrated that CT/RT followed by RS is not superior to exclusive CT/RT, although the results are feasible and safe. Reasonably, both approaches have associated toxicity problems at similar rates, although these are attributed to different mechanisms.[12]

Surgery for pathological response to treatment might have clinically relevant implications for definition of risk pattern of recurrence, individualized patient counselling and choice to administer adjuvant treatment.[12,13] Based on the close relationship between pathological response to neoadjuvant therapies and outcome, several efforts have been made in the last decade to modify dose and fractionation of cisplatin-based chemoradiation, as well as treatment time length or irradiated volumes.[14,15]

In order to improve LC by reducing the rate of regional failures at para-aortic lymph node level as well as in-field recurrences, a Phase I study [large field adjuvant radiotherapy in advanced cervical carcinoma (LARA-CC)-1 study] was set up by our Radiation Oncologists and Gynecologists group to investigate a regimen based on gross tumour volume (GTV)-accelerated fractionation and lymph node extended-field (LNEF) irradiation followed by RS.[16] The total dose of 45 Gy (2.25 Gy/fraction) to macroscopic tumour and 40 Gy (2 Gy/fraction) to lymph node stations was established as the recommended dose for the following study.[16,17] Indeed, LARA-CC-1 Phase II trial demonstrated that, at the recommended dose, complete pathological response (primary cervix and the nodes as well) to treatment was achieved in 38.6% of cases, a figure in line with previously reported results, but susceptible to further improvement through more advanced treatment delivery techniques. In this context, intensity-modulated radiotherapy (IMRT), where fluence of each beam is intentionally altered by the summation of hundreds of beamlets, could represent a valid strategy to satisfy clinical goals of target and normal tissue doses. IMRT has been shown to decrease the acute and late gastrointestinal (GI) toxicities owing to the conformality of dose distribution, confining the high-dose portions of radiation fields and reducing the absorbed dose in critical organs.[18] Promising results have been achieved by IMRT in patients with LACC in the intact disease setting and post-operatively.[19] Furthermore, conventional IMRT techniques allow the simultaneous delivery of different doses to different target volumes within a single fraction. This strategy is known as simultaneous integrated boost (SIB) technique (SIB-IMRT); it was introduced in several anatomical sites and is used to increase the fraction dose to the boost volume. SIB-IMRT keeps the dose to the elective volume at a low level and provides clinical and dosimetric advantages.[20,21]

To test the SIB-IMRT approach in patients with LACC, a Phase I–II study (LARA-CC-2) was launched in our radiotherapy unit (Catholic University, Campobasso, Italy) with the aim to investigate the feasibility and determine the recommended pre-operative IMRT dose of LNEF chemoradiation along with SIB dose escalation. Toxicity and outcome results are reported.

METHODS AND MATERIALS

Patient characteristics

Patients with The International Federation of Gynecology and Obstetrics (FIGO) stage IB2–IVA and histological proven invasive carcinoma of the cervix were eligible, regardless of pelvic lymph node status (Table 1). CT chest scan and abdominopelvic MRI were required for staging. Positron emission tomography (PET)-CT scan was not mandatory according to the study design. Patients were clinically staged on the basis of the pre-treatment workup by a multidisciplinary team including radiation oncologists, gynaecological oncologists and radiologists dedicated to gynaecological malignancies. Chemotherapy, abdominopelvic radiotherapy or any cancer treatment within the previous 3 years were considered as exclusion criteria.

Study design and end points

This was a prospective Phase I–II dose-escalation study (LARA-CC-2) approved by our institutional review board. All patients were required to provide a written informed consent agreeing to

Table 1. Patient characteristics

Patient characteristics	Number (%)
Whole series	19
Age, years, median (range)	46 (30–73)
FIGO stage	
IB2	3 (15.8)
IIB	10 (52.6)
IIIA	4 (21.1)
IIIB	2 (10.5)
Histotype	
Squamous	17 (89.5)
Adenocarcinoma	2 (10.5)
Tumour volume (cm)	
<4	1 (5.3)
≥4	18 (94.7)
Grade	
1–2	5 (26.3)
3	11 (57.9)
Not specified	3 (15.8)
Pelvic lymph node status[a]	
Negative	10 (52.6)
Positive	9 (47.4)

FIGO, The International Federation of Gynecology and Obstetrics.
[a]At MRI.

be submitted to all the procedures described and for their data to be collected. Primary end point was determination of the "recommended dose", otherwise known as the "maximally tolerated dose" (MTD). The "recommended Phase II dose" was defined as the lower dose level below the "highest administered dose", which corresponds to the dose associated with dose-limiting toxicity (DLT) in at least one-third of patients. Any treatment-related non-haematological adverse effects rated as grade ≥3 or any haematological toxicity rated as grade ≥4 by the Radiation Therapy Oncology Group acute (RTOG)/European Organisation for Research and Treatment of Cancer scale were defined as DLTs. If the DLT was not observed in the three patients at a set dose level, the trial proceeded to the next one, provided that 3 months of follow-up had occurred after the treatment for the third patient of the cohort. If a DLT occurred in one of the three patients at a given dose level, treatment of up to three additional patients at this dose level was required. If the DLT occurred in more than one patient of the three patients' cohort, dose escalation would stop, and the dose level below that would be considered as the MTD. As well, if a DLT occurred in two or more patients of the expanded six-patient cohort, dose escalation would stop, and the dose level below that would be considered as the MTD. Lastly, if a DLT occurred in less than two patients of the expanded six patient cohort, the trial proceeded to the next dose level.

Patients were enrolled in three consecutive boost dose levels, as reported in Table 2. Treatment was discontinued in patients with grade ≥3 non-haematological toxicity until grade 2 toxicity was resumed.

Secondary end points included the evaluation of pathologically assessed complete response (pCR), LC, disease-free survival (DFS) and OS.

Radiotherapy treatment planning

All patients underwent CT-based planning in a prone position using an up–down table device to displace small bowel volume from the treatment field. Patients with LACC received bowel preparation before simulation, and an empty rectum was required before CT simulation. To limit interfraction or intrafraction variability, a bladder-filling protocol (consisting of asking patients to void, drink 1 l of water 30–45 min before treatment and hold urine) was followed during CT simulation and subsequently before each treatment. After the administration of oral contrast medium, 4-mm CT images were obtained from the upper border of the T12 vertebral body to 3 cm below the ischial tuberosity.

Three clinical target volumes (CTV3, CTV2 and CTV1) were identified and contoured on CT simulation scan according to the guidelines by Taylor et al[22] and Lim et al[23] (Figure 1). CTV3 included primary tumour and positive lymph nodes (GTV), vagina (entire or upper half according to involvement), uterus, parametria, ovaries, obturator, external iliac, internal iliac, presacral (cranially to S2–S3 vertebrae) and common iliac lymph nodes (pelvic Level III) up to its apex in front of L3 vertebra.[24] The CTV3 upper field limit was chosen with the aim to irradiate lymph node areas normally excluded from the standard pelvic treatment yet potential sites of micrometastases.[16,25,26] CTV2 was considered as CTV3 excluding pelvic Level III; therefore, the CTV2 upper border of the field was kept at L4–L5 junction. CTV1 corresponded to GTV plus 1.5-cm margin into the uterus and included the positive lymph nodes, if present.

Planning target volumes (PTV3, PTV2 and PTV1) were defined as clinical target volumes (CTV3, CTV2 and CTV1) plus 8 mm.

Organs at risk, including the small bowel, rectum, bladder and femoral heads, were also contoured. Individual loops of small bowel were contoured separately from the axial slice situated 1 cm above the most superior slice containing the PTV and continued to its most inferior extent in the pelvis. The rectum being an organ was contoured as a solid continuous structure and was defined from the level of the sigmoid flexure to the anus. The bladder was similarly contoured as a solid continuous structure, whereas the bone marrow was not contoured.

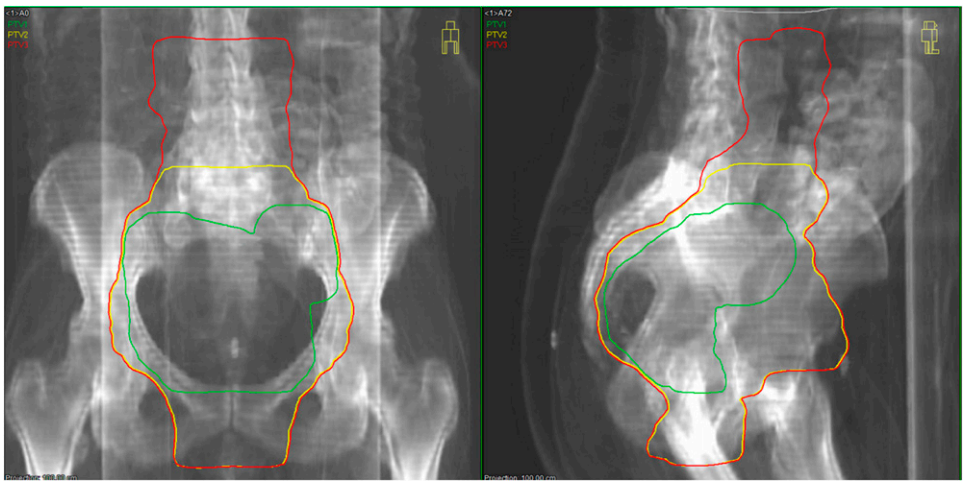
The extended-field SIB-IMRT technique was employed in all patients. Three dose levels were planned: Level 1 (PTV3: 40/2 Gy; PTV2: 40/2 Gy; PTV1: 45/2.25 Gy), Level 2 (PTV3: 40/2 Gy; PTV2: 45/2.25 Gy; PTV1: 45/2.25 Gy) and Level 3 (PTV3: 40/2 Gy; PTV2: 45/2.25 Gy; PTV1: 50/2.5 Gy). All treatments were delivered in 20 fractions. The PTV1 dose of 50 Gy in 2.5 Gy/fraction was selected at the beginning of the study as the highest dose level owing to small bowel tolerance, being the equivalent dose in 2 Gy/fraction for late effects (α/β ratio: 3) equivalent to 55 Gy (Table 2).[27] Dose specifications and nomenclature were

Table 2. Dose cohorts

Number of planned patients	Number of treated patients	Dose level	Dose (Gy)/fraction		
			PTV3[a]	PTV2[b]	PTV1[c]
3	6	I	40/2	40/2	45/2.25 (47.25)[d]
3	7	II	40/2	45/2.25 (47.25)[d]	45/2.25 (47.25)[d]
3	6	III	40/2	45/2.25 (47.25)[d]	50/2.50 (55.0)[d]

EQD2, equivalent dose in 2 Gy/fraction; PTV, planning target volume.
[a]PTV3: pelvic lymph nodes up to L3 plus margin.
[b]PTV2: pelvic lymph nodes up to L5 plus margin.
[c]PTV1: macroscopic disease plus margin.
[d]EQD2 for late effects (α/β ratio: 3).

Figure 1. Planning target volumes [PTV3 (red isodose), PTV2 (yellow isodose), PTV1 (green isodose)] are shown on orthogonal digital reconstructed radiographs. For colour image see online.



according to the International Commision on Radiation Units and Measurements report 83. Dose–volume prescriptions are shown in Table 2. Doses were converted into their radiobiological equivalence to determine the tolerances. Target planning constraints used were reported in Table 3. All IMRT plans consisted of seven co-planar equispaced fields with 6-MV photons. All plans were generated with Oncentra® MasterPlan treatment planning system (Oncentra Masterplan) and delivered by an Elekta Precise Linear Accelerator (Elekta Ltd, Crawley, UK).

Owing to the complexity of treatment, all plans underwent pre-treatment verification. The delivered doses were measured using the seven 29 ion chamber array.[28,29] PTW VeriSoft® software v. 4.0 (VeriSoft software; PTW, Freiburg, Germany) was used to carry out a comparison of measured *vs* calculated dose distributions. The gamma index evaluation was employed. If the percentage of points fulfilling gamma index criteria exceeded 95% (3% for dose criterion and 3 mm for the distance to agreement criterion), the pre-treatment dosimetry was considered optimal. For quality assurance through treatment planning and delivery, two independent checks (IC1 and IC2) were performed by medical and physics staff;[30] daily set-up reproducibility was checked.[31] Portal images before irradiation were acquired on virtual orthogonal beams and deviations >3 mm in the isocentre position were immediately corrected as previously described.[31]

Table 3. Planning constraints

Region of interest	Constraint
PTV	$V_{95\%} > 95\%$ $V_{107\%} < 2\%$
Small bowel	$V_{15} < 120\ cm^3$
Rectum	$V_{50} < 50\%$
Femoral heads	$V_{50} < 10\%$

PTV, planning target volume; V_{15}, volume receiving 15 Gy; V_{50}, volume receiving 50 Gy; $V_{95\%}$, volume receiving 95% of the prescribed dose; $V_{107\%}$, volume receiving 107% of the prescribed dose.

Chemotherapy

In the first and last weeks of radiotherapy, cisplatin (20 mg m^{-2}, 2-h intravenous infusion, Days 1–4) and 5-fluorouracil (1000 mg m^{-2}, 24-h continuous intravenous infusion, Days 1–4) were administered. In case of relapse/progression of disease, patients were considered for salvage treatment on a case-by-case basis.

Surgery

4–6 weeks after completion of CT/RT, objective response to treatment was evaluated according to response evaluation criteria in solid tumour criteria; patients achieving response to treatment were triaged to radical hysterectomy (RH) according to Querleu and Morrow[32] and pelvic ± aortic lymphadenectomy within 6–8 weeks from the completion of CT/RT. Aortic lymphadenectomy was performed in case of (i) positive pelvic lymph nodes at frozen section analysis routinely performed during completion surgery, (ii) positive pelvic lymph nodes at imaging within initial staging workup and (iii) intraoperatively assessed suspicious aortic lymph nodes. In the case of stable disease or progression rescue, chemotherapy or chemoradiation was allowed.

Pathological response to treatment was evaluated based on the examination of uterus, vaginal cuff, parametrium, pelvic and aortic lymph nodes: residual disease at any site was expressed in millimetres, and response was defined as complete [absence of any residual tumour after treatment at any site level: pathological complete response (pCR)], microscopic [persistent tumour foci of ≤3 mm maximum dimension microscopic pathological response (microPR)] and macroscopic (persistent tumour foci of >3 mm maximum dimension).[8]

Toxicity assessment

Radiation-related toxicity was assessed prospectively according to the RTOG criteria. Acute adverse events were defined as those adverse events occurring from Day 1, or commencement of radiation therapy, up to Day 90. Bowel, bladder, ureteral or vascular injuries, as well as estimated blood loss >500 ml, were defined as operative complications. Any adverse events occurring within or

after 30 days from surgery were defined as early and long-term post-operative complications, respectively. Surgical morbidity was classified according to the Chassagne grading system. Patients underwent quarterly follow-up for the first 2 years and half-yearly thereafter. Even in the case of documented relapse or disease progression, late toxicities were continuously monitored.

Statistical analyses

Medians and life tables were computed using the product limit estimate by Kaplan–Meier method, and the log-rank test was used to assess the statistical significance. LC was calculated from the date of surgery to the date of the inside field relapse/progression of disease or the date last seen. Likewise, DFS was calculated from the date of surgery to the date of relapse or the date of the last follow-up; OS was calculated from the date of diagnosis to the date of death or the date of the last follow-up. Statistical analyses were performed using Systat v. 10.2 (Systat for Windows, Software Inc. 2002, San Jose, CA).

RESULTS

Patient population

This study included 19 consecutive patients with LACC in dose cohorts. Population characteristics and dose level details are reported in Tables 1 and 2, respectively. Nearly 60% (11 of 19) had a PET-CT scan in their workup, although PET-CT was not mandatory, according to the study design.

Compliance and toxicity

At Level I, one patient out of three had GI grade 3 toxicity (emesis, nausea, diarrhoea); therefore, additional three patients were recruited, and all of them completed CT/RT without any DLT. All Level I patients ($n = 6$) completed CT/RT and underwent RS. Based on these findings, dose Level II was opened for accrual: one out of three patients developed grade 3 proctocolitis with emesis, nausea, diarrhoea and was successfully treated by parenteral medical therapy. This patient also suffered from a herpes zoster virus infection during the time interval between CT/RT

Table 4. Acute toxicity after chemoradiation[a]

Toxicity	Grade	Level I ($n = 6$), PTV3 = 40 Gy, PTV2 = 40 Gy, PTV1 = 45 Gy	Level II ($n = 7$), PTV3 = 40 Gy, PTV2 = 45 Gy, PTV1 = 45 Gy	Level III, ($n = 6$), PTV3 = 40 Gy, PTV2 = 45 Gy, PTV1 = 50 Gy	Whole series ($n = 19$)
		Number of cases	Number of cases	Number of cases	Number of cases (%)
Lower gastrointestinal	0	1	0	0	1 (5.3)
	1	2	0	1	3 (15.8)
	2	2	6	3	11 (57.9)
	3	1	1	2	4 (21.1)
Upper gastrointestinal	0	6	6	5	17 (89.5)
	1	0	0	0	0
	2	0	1	1	2 (10.5)
	3	0	0	0	0
Genitourinary	0	1	3	1	5 (26.3)
	1	3	4	2	9 (47.4)
	2	2	0	3	2 (10.5)
	3	0	0	0	0
Skin	0	2	1	2	5 (26.3)
	1	1	4	2	7 (36.8)
	2	3	2	2	7 (36.8)
	3	0	0	0	0
Haematological	0	3	2	3	8 (42.1)
	1	1	0	0	1 (5.3)
	2	1	2	1	4 (21.1)
	3	1	3	1	5 (26.3)
	4	0	0	1	1 (5.3)

PTV, planning target volume.
[a]The two patients with severe genitourinary toxicities recorded in the perioperative period are described in the text; acute toxicity was graded according to the Radiation Therapy Oncology Group acute criteria. Number of patients are reported per level and in the whole series.

completion and RS. Level II cohort was thus expanded to include three patients plus an additional one who was treated while monitoring of toxicity was ongoing in the preceding three patients. All Level II patients ($n = 7$) completed CT/RT and were triaged to RS. At level III, one patient presented grade 3 GI toxicity (emesis, nausea, diarrhoea) requiring intravenous fluid intake until resolution, thus leading to the expansion of dose Level III ($n = 6$). Since the second patient developed grade 3 GI, the study was closed, and the recommended dose was established as that corresponding to dose Level II. Details about the pattern and severity of acute toxicity are presented in Table 4. The predominant DLTs were GI. Grade ≥3 lower GI toxicity occurred in 21% of patients and consisted mainly of dehydration secondary to nausea, vomiting or diarrhoea, which required intravenous fluid administration. No patients presented grade ≥3 genitourinary (GU) or skin acute toxicity.

Grade ≥3 haematological toxicity occurred in 31.5% of patients, and one dose-limiting leukopenia (grade 4) was recorded in a patient affected also by grade 3 GI toxicity. All reported toxicities occurred within 10–20 days after the end of chemoradiation.

As far as intraoperative complications are concerned, we documented only one bladder injury (5.3%) in a patient treated at the dose Level III; the lesion was managed intraoperatively without major intervention.

In the post-operative period, 2 patients (10.5%) experienced the following grade 3 GU complications: one patient had fever on the fourth day after surgery, and abdominal CT scan showed three lymphocysts, of which the largest one (maximum axial diameters = 60 × 25 mm) was located in the right pelvis and surrounded by the iliopsoas muscle, the external iliac vessels and laterally by the right side wall of the bladder. Since the patient was complaining about chronic abdominal pain, the largest lymphocyst was removed through minilaparotomy 5 months later. 9 months after surgery, the patient developed grade 1 bilateral ureteral dilatation with normal renal function, in the absence of signs of disease up to 26 months since diagnosis.

The second patient, suffered from ureteral intra-abdominal leakage and underwent laparotomy with permanent percutaneous nephrostomy which permitted subsequent normal renal function (grade 3). Also in this case, there was no sign of disease after 14 months from diagnosis.

Concerning long-term toxicity, the actuarial 2-year (≥grade 2) GU toxicity-free survival was 88.8%; neither grade ≥2 GI complications nor skin or mucosal toxicities were observed (data not shown).

Treatment planning details

According to dosimetric constraints, target coverage was met in all patients. Planning constraints for normal tissues were always respected with the exception of small bowel: only two patients respected V_{15} <120 cm^3 constraint; on the contrary, 89.5% (17 of 19) of patients largely exceeded the V_{15} <120 cm^3 constraint (median value=268.9 cm^3, range=96–481 cm^3). Three of the four patients presenting severe GI toxicity did not meet the quantitive analysis of normal tissue effects in the clinic (QUANTEC) small bowel constraint V_{15} <120 cm^3 (Pearson χ^2: $p = 0.440$).

Pathological response

RH was possible in all patients; laparotomic approach was performed in 68.4% of cases. Systematic pelvic lymphadenectomy was performed in all patients with a median number of removed lymph nodes of 27 (range = 15–57). 11 (57.9%) patients were also submitted to aortic lymphadenectomy (median number of removed lymph nodes = 8, range = 3–54).

Pathological complete response (CR) rate combining both pCR and micro-pPR rates was 63.1%, with 6 (31.6%) patients showing pCR to treatment and 6 (31.6%) showing microPR. Macroscopic response was observed in 7 (36.8%) cases.

Outcomes and survival

As of October 2014, median follow-up period was 24 months (range = 9–60 months). Relapse/progression of disease was observed in 4 of 19 patients (21.1%): in particular, 2 cases (10.5%) developed extrapelvic recurrence; 1 patient had lung metastasis and underwent resection and subsequently developed brain metastases which were irradiated; and 1 patient had mediastinal and supraclavicular lymph node relapse and received rescue chemotherapy. Finally, two patients (10.5%) developed mixed recurrences (local recurrence and distant metastases). There was no case of recurrence/progression occurring exclusively in the pelvic region.

The 2-year LC was 89.5% (median LC: not reached), while the 2-year DFS was 82.0% (median DFS: not reached). Death due to disease was recorded in 2 of 19 patients (10.5%), and the 2-year OS was 88.8% (median OS: not reached).

DISCUSSION

The working hypothesis supporting the present study was mainly based on our previous experience with pre-operative GTV-accelerated fractionation and LNEF irradiation (up to L3 vertebra) delivered by the three-dimensional (3D) technique.[16,17] Despite the dose escalation, studies[16,17] proved the safety and potential efficacy of 45 Gy concomitant boost plus 40 Gy enlarged field chemoradiation in patients with LACC. However, the Phase II study failed to show an increase in the rate of pCR to treatment.

With the aim to deliver over a short time interval, a higher radiotherapy dose at sites of macroscopic disease without increasing the rate/severity of damage to normal tissues associated with the 3D approach, escalating doses of SIB-IMRT were investigated in the present study. This analysis represents, to our knowledge, the first evaluation of LNEF-SIB-IMRT as pre-operative treatment of patients with LACC.

Results from the current Phase I study established the dose of 45 Gy to macroscopic tumour, positive lymph nodes, common iliac lymph nodes up to the cranial margin of L5 vertebra, and 40 Gy to common iliac lymph nodes in front of L3 up to its apex, as the recommended dose for further evaluation.

Contrary to results expected from the use of IMRT techniques in the exclusive chemoradiation as well as adjuvant setting,[19,33–35] we could not escalate the dose at levels higher than those reached with the 3D approach; indeed, acute GI toxicity represented the

major limitation to dose escalation and were documented at rates similar to those observed with the 3D technique in the same clinical setting.[16,17] Reasonable caution has to be taken in interpreting these data given the small sample size of current series which included a slightly higher fraction of patients bearing pelvic lymph node involvement at imaging, a condition which could have implied the requirement of higher dose target volume and consequently larger small bowel irradiation.

In this context, it has also to be underlined that, even though a controlled filling protocol was applied and daily portals enclosed in the plan have been performed before treatment, no daily cone beam image guidance was available, thus possibly determining an excessive amount of normal tissue falling into the high-dose areas of treatment as the tumours regressed over the course of treatment. In addition, although carefully educated, we cannot be certain that the patients have respected the daily controlled filling protocol for bladder and rectum. As pelvic organ motion seems to be patient specific, individualized PTV margins and adaptive image-guided radiotherapy (IGRT) strategies have also been recommended to ensure target volume coverage while increasing OAR sparing. Although these strategies are promising, they need significant validation before they can be adopted into clinical practice. In a very recent article by a French group,[35] authors delivered 50 Gy in the PTV1 and 60 Gy in the PTV2 simultaneously in 28 fractions (5 fractions a week). Indeed, the volumes irradiated were considerably smaller than ours; in particular, our boost volume corresponded to GTV plus 1.5-cm margin into the uterus and included the positive lymph nodes, if present, while Mouttet-Audouard et al[35] boosted on GTV plus a 4-mm margin. Moreover, PTV margin was larger in our experience than in the French study (8 *vs* 3 mm), resulting in a larger amount of normal tissue falling into the high-dose areas of treatment.

As far as perioperative toxicity is concerned, we documented only two cases of post-operative urinary complications with an overall rate of 10.5% in keeping with the corresponding figure (29%, mostly urinary) obtained in the 3D dose escalation as well as Phase II study in a similar setting.[16,17] Whether this observation could be ascribed to a lower impact of IMRT on tissue tropism with subsequent easier surgical procedures remains difficult to be ascertained: in fact, the relevance of surgeons' skilfulness and learning curve in RS cannot be underestimated.

Conversely, our late toxicity results are hardly comparable to those reported in the setting of intact disease not only because of the evident differences of study design and population, but extension of volumes encompassing both positive pelvic lymph nodes and primary tumour at the highest dose, and upper limit of the irradiation field at cranial margin of the third lumbar vertebra, could imply a more than standard irradiation of the small intestine. It has to be underlined that the small bowel constraint normally reported in literature (*i.e.* the 120 cm^3 volume of small bowel receiving >15 Gy, in order to minimize severe acute toxicity)[36] remained unsatisfied in 89.4% of cases.

Finally, the treatment time (4 weeks) could have impaired the adequate small bowel repopulation, thus leading to a negative impact on damaged tissue repair. As far as clinical outcome is concerned, we reported a rate of pCR to treatment of 63.1% and a 2-year LC rate of 89%, which is systematic with previously reported data.[8,16,17]

In conclusion, SIB-IMRT, as delivered, was unable to safely escalate dose beyond those achieved with 3D conformal radiotherapy given acute GI toxicity; therefore, we established the dose of 45 Gy to macroscopic tumour, positive lymph nodes, common iliac lymph nodes up to the cranial margin of L5 vertebra, and 40 Gy to common iliac lymph nodes in front of L3 up to its apex, as the recommended doses for further evaluation of IMRT extended-field chemoradiation plus simultaneous integrated boost in the pre-operative treatment of patients with LACC.

Since interfractional and intrafractional shifts, possibility of significant tumour regression during treatment, economic impact of increased planning and technological requirement can represent potential concerns in IMRT approach to patients with LACC, further studies with larger sample size, longer follow-up and image guidance are needed. A cautious approach to this kind of treatment in the absence of adaptive IGRT strategies needs to be validated before they can be adopted into clinical practice.

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