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A survey on staging and treatment in uterine cervical carcinoma in the Radiotherapy Cooperative Group of the European Organization for Research and Treatment of Cancer

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Abstract

Background: The treatment outcome of advanced stage uterine cervical carcinoma remains unsatisfactory. In order to elaborate a novel trial within The Radiotherapy Cooperative Group (RCG) of the European Organization for Research and Treatment of Cancer (EORTC), we conducted a survey in 1997–1998 to determine the variability of pre-treatment assessment and treatment options. The variability of choosing surgery, defined radiation therapy techniques and chemotherapy are investigated, as well as the center's choices of future treatment strategies.

Methods: Fifty two of 81 RCG centers from the RCG have participated in the survey. As one would expect, there is a large variation in the techniques used for pretreatment evaluation and treatment options. There is no 'standard' for reporting acute and late side effects. Chemotherapy is used neither systematically nor uniformly, and some centers continue to use neadjuvant chemotherapy modalities.

Results: Furthermore, the survey reveals that there is a strong demand for the reduction of overall treatment-time, for clinical investigation of novel combined modality treatment strategies, especially chemo–radiation therapy, and also for the use of new radiation sensitizers.

Conclusion: We conclude that a more homogeneous approach to the pretreatment evaluation as well as treatment techniques is required in order to allow adequate quality control in any future trial of the RCG in the EORTC.

Keywords: Cervix cancer; Pretreatment evaluation; Surgery; Chemo–radiotherapy

1. Introduction

The Radiotherapy Cooperative Group (RCG) of the European Organization for Research and Treatment of Cancer (EORTC) is conducting a variety of trials for different tumor localizations. However, gynecological tumors are currently not the subject of any ongoing trial, notwithstanding the fact that radiation therapy plays a major role in the treatment of cervical carcinoma. There is one ongoing intergroup trial (EORTC-GCCG) investigating the usefulness of the addition of cisplatin-based chemotherapy to postoperative radiation therapy in stages Ib and IIa cervical carcinoma after radical hysterectomy and complete lymphadenectomy. There is not a single trial addressing the question of adequate treatment for locally-advanced cervical cancer (LACC), i.e. FIGO stages IIb, IIIa and IIIb. This is difficult to understand, facing the multitude of open questions related to the optimal investigational approach and therapeutic management of cervical carcinoma.

In order to define whether there is an interest within the RCG to study new therapeutic concepts in LACC, we sent a questionnaire to radiotherapy groups which are listed as participating members of the RCG. This questionnaire is designed to determine the general feasibility of a trial in Europe, taking into consideration the decreasing number of patients with LACC addressed to radiation therapy departments. Finally, we try to define which questions have to be given priority in future trials. Special attention is dedicated to the concept of the association of chemotherapy and ionizing irradiation, the concept of the impact of treatment duration on local control, and to the use of 'new' radiosensitizers. The answers on this questionnaire are analyzed and discussed, taking into account the 'guidelines' and/or 'evidence' reported in currently published literature.

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2. Methodology

The questionnaire was designed in 1997 and sent to 81 RCG centers. The questionnaire contains general questions related to the number of patients (on a yearly basis) treated in the individual RCG centers, their stage distribution, the techniques used in the pretreatment evaluation and the therapeutic options considered as 'standard'. For the latter, specific questions address the relative role and sequence of the four basic therapeutic options, namely surgery, chemotherapy, external irradiation and brachytherapy. Regarding external irradiation, special attention is given to technical details related to the treated volumes, number of fields used, total dose and dose/fraction, and prescription point. The importance of brachytherapy is reported again with some details on dose-rate, number of applications, in vivo dosimetry and timing with external treatment. The questionnaire aims to define the relative importance of chemotherapy, the type of chemotherapy, i.e. neoadjuvant, concomitant or sequential, and the most frequent drugs used. One question concerns the toxicity scale used to report the acute and late side effects.

Finally, bearing in mind the more general question raised by the RCG, i.e. the feasibility of a trial within the EORTC, the centers are asked if they will participate in a general effort to run such a trial. The RCG members are asked to state if they are interested in investigating the importance of the package-deal concept (the time factor), the importance of chemotherapy or the use of 'new' sensitizers.

3. Results

Fifty two centers out of 81 (64%) answered the questionnaire. The average number of patients/year addressed to the departments of radiation–oncology is 48 (median value 24, range 5–600). These patient numbers are listed in Table 1 according to stage distribution. Considering LACC (defined as IIb–IIIa–IIIb), we recorded a mean value of 25 (median 15, range 1–358) new patients/center per year.

3.1. Pretreatment evaluation and staging

One of the first important questions is related to T and N staging. For the clinical evaluation of local tumor infiltration, routine cystoscopy is rated high (89%) alongside the digital gynecological examination, but only 56% of the centers mention routine rectoscopy. The use of transvaginal ultrasound has not been recorded in this questionnaire.

Table 1
Distribution of number of patients/stage per year

Stage	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
Mean[a]	7	14	6	9	4	12	3	3
Median[a]	3	6	4	6	3	6	2	3

[a] Number of patients/center per year.

Ninety four percent of the centers reported practicing nodal staging. Evaluation of nodal involvement is mainly performed with computed tomography (CT) (85%) and nuclear magnetic resonance (NMR) (50%). Patients are less frequently submitted to surgical staging (35%). The technique used for surgical staging is laparatomy (23%), or coelioscopy (21%). Unfortunately, no data are available in order to determine how much of these surgical stagings are associated with a radical hysterectomy, and the rate of surgical staging in respect of stage.

Lymphangiography (LAG) as part of the routine pretreatment work-up has been reported by only seven centers (14%).

3.2. Treatment options and treatment sequence

3.2.1. Surgery

The possible treatment policies include surgery, external irradiation, brachytherapy and chemotherapy. As illustrated in Fig. 1a, the use of curative surgery as the initial approach to treatment decreases as the FIGO stage increases. The importance of radiotherapy (Fig. 1b) and brachytherapy as primary treatments (Fig. 1c) progressively increases with higher FIGO stages. Sixteen centers use surgery as part of the treatment for stage IIb, six for stage IIIa, five for stage IIIb, and ten centers for stage IVa. Moreover, four centers record surgery as upfront treatment in IIb, one in IIIa and four in IVa. Surgery is the preferred first-line treatment modality in stage Ia (83%), Ib (73%) and IIa (60%). Surgery includes at least hysterectomy with or without node sampling or node dissection. More details on the surgical procedure are not available.

3.2.2. External beam irradiation

External irradiation is more likely to be used as a first-line treatment for IIb and higher stage disease. The use of radiation as a first-line treatment modality or as part of a combined treatment-approach in respect of stage is summarized in Table 2.

Thirty out of 52 centers (58%) are using 2D plannification, i.e. using one single CT-slice at the center of the fields, whereas 23 (44%) are using 3D (a series of CT-slices). Six out of 52 centers (12%) use neither 2D nor 3D for dose-calculation for external beam radiation therapy. Five out of these six centers are located in western Europe. Five centers use 2D or 3D according to the complexity of the case. The median dose for external irradiation is 45 Gy, but with a range of 36–70 Gy according to the center and tumor stage. The median number of fractions/week is five (range 5–10) with a median dose/fraction of 2 Gy (range 1.5–2 Gy). This external treatment is usually given by a four-field box technique on the pelvis (85%). However, in eight centers, an AP–PA field is still used to cover the pelvic volume. If para-aortic nodes are considered as the target, these nodes are covered by AP–PA fields by the majority of the centers (67%). The median number of fields treated daily for the

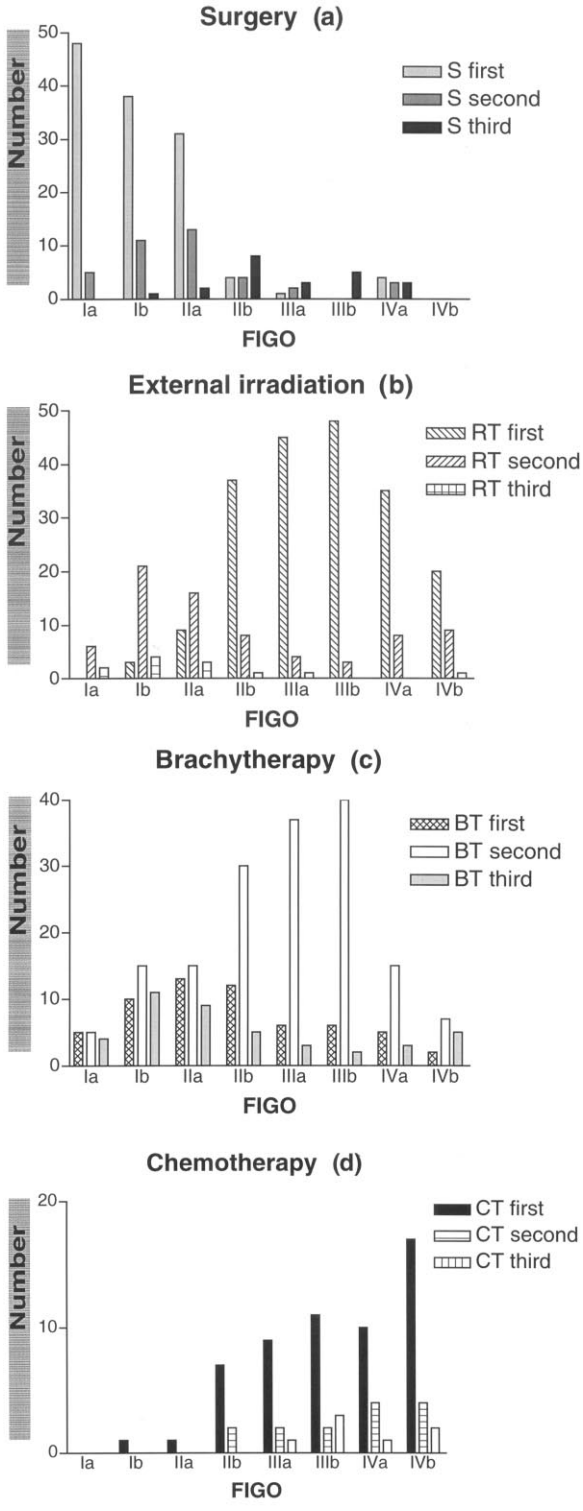

Fig. 1. Treatment sequence according to FIGO stage. The centers were asked to report the curative treatment modalities in function of priority. Places of (a), surgery; (b), external radiation therapy; (c), brachytherapy; and (d) chemotherapy in the treatment sequence.

pelvic volume is four, and two for the para-aortic volume. The para-aortic nodes are never treated by five centers (10%). Forty-six centers (89%) are covering those nodes if they are found to be positive during pretreatment evaluation, whatever the technique used (CT, NMR or surgical staging), and 22 centers (42%) are including those nodes within the target volume if the pelvic nodes are positive.

Table 2
Use of external irradiation as first-line (A), or as a component of treatment (B), according to FIGO stage[a]

RTH	Ia	Ib	IIa	IIb	IIIa	IIIb	IVa	IVb
A	–	–	–	71	87	92	67	39
B	15	54	54	89	96	98	83	58

[a] Number of centers reported in % of total number.

3.2.3. Brachytherapy

Brachytherapy is used to boost external radiation especially in stages IIb, IIIa and IIIb (58, 71 and 77%, respectively). In Table 3, we have summarized the percentage of centers using brachytherapy as part of the treatment according to FIGO stage. The dose specification for the brachytherapy is 'Point A' in 29 centers (56%), an isodose envelope in 18 centers (35%), and three centers (6%) do not really specify their reference point. Brachytherapy is essentially applied after the completion of the external irradiation (35 centers, 67%), but in 16 centers (31%) it is given during irradiation, and for seven of these centers there is at least one brachytherapy application after the end of the external irradiation. The centers have reported a range of fractions for the brachytherapy of 1–8, with a median value of two for LDR and three for HDR. The median cumulative dose at the reference point is tailored according to stage and to the external radiotherapy dose. Brachytherapy is subdivided according to the dose-rate, resulting in high dose-rate (HDR, >12 Gy/h), medium dose-rate (MDR, 2–12 Gy/h) and low dose-rate (LDR, <2 Gy/h). A majority of centers (64%) are using LDR, 31% use HDR, 4% use MDR and one center uses both LDR and HDR. The ranges and median values at the reference point for the individual stages Ia, Ib, IIa, IIb, IIIa, IIIB, IVa and IVb are listed in Table 4 according to the dose-rate. The progressive reduction in dose applied by brachytherapy for increasing stages reflects the growing importance of the external irradiation component. In vivo dosimetry at the level of the bladder and the rectum is rarely performed, 13 and 31% of the centers reporting it, respectively.

Table 3
Use of brachytherapy as first-line or as a component of 'curative' treatment according to FIGO stage[a]

Ia	Ib	IIa	IIb	IIIa	IIIb	IVa	IVb
27	69	71	90	88	92	44	27

[a] Number of centers reported in % of total number.

Table 4
Range and median values in Gy of brachytherapy doses according to stage and dose-rate[a]

	Ia	Ib	IIa	IIb	IIIa	IIIb	IVa	IVb
MDR[b]	–	21	21	24	24	24	24	–
HDR	10–28	10–30	10–35	10–35	9–40	9–40	10–40	10–40
Median	17	17	18	18	18	20	18	17
LDR	20–70	20–80	20–70	10–70	10–60	10–60	10–50	19–60
Median	60	40	45	40	35	35	30	20

[a] The ranges in total dose at the reference point are explained by variation of the relative importance of brachytherapy in the treatment protocol in the different centers.
[b] MDR-data bases on reports from two centers.

3.2.4. Reporting radiation side effects

Radiation side effects are reported using different grading scales; the more recently published LENT/SOMA has not gained wide acceptance since six centers (12%) are using this scale for acute side effects and nine centers (17%) for late side effects. The French–Italian glossary [5] is more frequently used (acute effects: 19 centers, i.e. 37%; late effects: 24 centers, i.e. 46%). This is followed by the World Health Organization (WHO: l7 acute and 13 late) and the Radiation Therapy Oncology Group (RTOG: l4 acute and 13 late) grading systems. Fifteen centers use more than one grading system to report side effects, i.e. they mix up a scale for early effects from one group with a scale for late effects from another group. Thirty five centers (67%) consistently use the grading system issued from the same group (mainly the French–Italian glossary) to report acute and late effects.

3.2.5. Chemotherapy

Chemotherapy is divided into neoadjuvant (prior to definitive local treatment, such as surgery or radiotherapy), concomitant (synchronous combination with external irradiation) and sequential (alternating with external radiation therapy). Neoadjuvant chemotherapy is used by 11 centers, concomitant chemo–radiation therapy by 15 and sequential by six. The indications for chemotherapy are FIGO stage-dependent. None of the centers report any form of chemotherapy in stage Ia compared to 23 centers, i.e. 44%, in the case of stage IVb. Neoadjuvant chemotherapy is more frequently applied in more advanced diseases. For example, seven centers report neoadjuvant chemotherapy for stage IIb, nine for stage IIIa and eleven for stage IIIb. There is a general trend to introduce more and more chemotherapy with higher stage disease. Cisplatin is the most commonly used chemotherapeutic agent.

3.3. New approaches

One of the primary aims of the present questionnaire is to determine the interest in the RCG within the EORTC in conducting a phase III trial. Forty one out of 52 centers (79%) are willing to participate to a prospective trial. Most of the latter are interested in a trial investigating the importance of chemotherapy in LACC, especially in the setting of concomitant use of chemotherapy (33 centers = 64%). It should be noted that the questionnaire was addressed to the centers before the data on the effect of cisplatin in LACC was available.

The question relating to the importance of total treatment duration (reducing the package-deal concept) was found to be a worthwhile test in a randomized trial in 25 centers (48%). The concept of innovative approaches and especially the testing of 'new' sensitizers in a phase I/II trial was accepted by 29 centers (56%), with the majority (16/29) choosing taxol. Other possible 'new sensitizers' generating interest in the questionnaire were gemcitabine (11 centers), CPT-11 (eight centers), iodo-deoxy-uridine (five centers), tirapazamine (four centers). Hydroxyurea was not reported as an interesting agent to be tested.

4. Discussion

This survey, established initially to evaluate the feasibility of a trial within the EORTC-RCG in LACC, results in an interesting amount of information concerning staging and treatment habits in Europe. The first relevant point is the rate of response to the survey. Sixty four percent of the centers have answered to the questions raised, and therefore this survey yields a representative estimation of staging and treatment habits in the RCG centers of the EORTC. The most important information is the large variation in patient care, and this, although expected, has not yet been documented.

4.1. Pretreatment evaluation and staging in cervical cancer

Tumor stage (T) is, with nodal stage (N), one of the most important prognostic factors. To assess T and N stage, an extensive local and regional examination is necessary. T can easily be assessed by digital rectal and vaginal examination under anesthesia. The clinician should not only report tumor stage, but also tumor size, because the latter behaves as an independent prognostic factor, as shown in a recently published multivariate analysis [1]. However, tumor size is rarely reported.

We initially expected a large majority of centers reporting

both cystoscopy and rectoscopy as routine procedures for clinical evaluation of local tumor extent. While cystoscopy is rated in nearly all centers, only slightly more than half of them are reporting rectoscopy as a routine procedure.

One of the most challenging problems in the diagnostic procedure is to detect lymph-node disease, as its presence changes the prognosis, and hence, treatment. The literature reports a 20–40% discrepancy between surgical and clinical staging [31], and some authors claim that there is a role for debulking of pelvic node metastases, as this debulking may result in increased cure-rates [9,31]. Most of the centers report a procedure for the detection of lymph-node metastases, but there is a large variation in the techniques used. Surgical staging is performed in about one quarter of the centers. If pelvic lymph-node staging is performed surgically, retroperitoneal staging should be preferred as it is less morbid than transperitoneal staging [9,31]. Our questionnaire does not allow us to assess whether lombo-aortic sampling is performed in centers which mention a surgical procedure.

If non-surgical techniques are used for the assessment of lymph-node stage, one has to mention that the lymphangiography (LAG) remains the best available technique, although this procedure is rarely performed in the present day. This is mainly due to the lack of expertise, and therefore the technique risks being discarded as part of the routine diagnostic work-up. Only a minority of centers (14%) in our study use LAG for nodal status evaluation, most of them use CT or NMR, which are known to be less sensitive and specific than LAG. However, as shown by the Gynecologic Oncology Group (GOG), LAG has a sensitivity of 79% and specificity of 73%, whereas CT and ultrasound have sensitivities of 34 and 19%, and specificities of 96 and 99%, respectively [15]. The importance and utility of LAG, especially if external radiotherapy is planned, is confirmed by the work of Bonin et al., who demonstrated that bony landmarks are not an adequate substitute for LAG for the localization of pelvic lymph nodes [3]. Some authors are convinced that LAG remains the tool of choice in order to define target volumes and field limits for external radiation [3].

In conclusion there is a clear shift in diagnostic work-up, with a decrease of the importance of LAG to 14%. This can be compared with the 11–18% reported in the patterns of care study of Perez and Montana [25,27]. The reduction in the use of LAG corresponds with an increase to 85% in the use of CT (compared to 70% in the patterns of care study), although a poor correlation between CT and surgical staging has been documented (50–60%). In our study, 50% of the centers are using MRI, although the accuracy of MRI in detecting metastatic lymph nodes has not been established. Surgical nodal staging is performed in 18 centers, and hence, declining frequency in the use of LAG is not compensated by a more frequent use of surgical staging. The shift towards CT and/or MRI in the staging procedure, and away from LAG, results in a potential loss of accuracy of the diagnostic work-up. This has to be considered in reviewing the therapeutic results and comparing these with the historical series, in which LAG was considered as standard.

4.2. Treatment options and treatment sequence

4.2.1. Surgery

Most of the centers are advocating curative surgery for early stage cervical cancer. Our results are therefore similar to a survey performed in the USA, highlighting a progressive increase in the implication of gynecological oncological surgeons in the primary treatment of early cervix cancer. In our survey, radiation therapy seems to be less frequently used for early stage disease, decreasing from 70 to 60.3%, as either the only treatment or in combination with other treatment modalities [34]. This trend in stage Ib–IIa cervical cancer seems not to be evidence-based, taking into account the randomized study reported by Landoni et al. [22]. That trial compares curative surgery to curative radiation therapy in early stage cervix cancer. The 5-year actuarial survival is identical in both arms of the trial (83%), but there is a significant difference favoring external radiotherapy as far as severe morbidity, especially urological, is concerned (28 vs. 19%). The combination of surgery and radiotherapy yields the highest morbidity, especially regarding late-responding normal tissues. Therefore, optimal selection is required for surgery, leaving only premenopausal women with normal ovarian function and with cervical diameters of less than 4 cm as potential candidates for primary surgery, assuming there is no suspicion of nodal involvement [10,22]. Furthermore, emphasis should be put on total cost in clinical practice, with a net increase if hysterectomy and postoperative radiotherapy are compared to radiation therapy alone in stage Ib–IIb [8].

It is noteworthy that a number of centers report surgical options in LACC even as a first-line curative treatment in the present survey. To our knowledge, there is, however, no evidence supported by any randomized trial suggesting that such an aggressive surgical approach would yield any benefit in patients who will need subsequent high-dose radiation therapy.

4.2.2. Radiotherapy

Three different aspects of radiation therapy deserve special attention: the definition of the target volume, the volumes to be treated by external radiation and the brachytherapy.

To obtain optimal treatment, one needs to adequately define the target volume. A CT-guided plannification (either 2D or 3D), seems to be performed in nearly all centers. Only six centers are not using CT at all. This reflects the general quality of the treatment planning. Kim et al. have shown that the most common site of an inadequate margin is located at the position of the rectal block resulting in a geographical miss in 39–50% of the patients in stage Ib–IVa [20]. This is

followed by the posterior margin in 25–32% of the cases. If the anterior surface of the sacrum is included, a dramatic drop to almost no geographical misses at the posterior border of the lateral fields is observed, suggesting that a four-field box technique with customized blocking should not be used unless a dedicated CT is available [20]. In the present survey, six centers do not use CT-guided plannification, and four of them are treating the pelvic volume with a four-field box technique. The posterior limit and the use of individualized blocks in the lateral field have not been inquired in the present survey, and therefore we cannot really assess if there is an increased risk of geographical miss. A second question relates to the volumes to be treated with external radiation therapy, especially the irradiation of para-aortic nodes. The RTOG trial demonstrates a 10-year survival benefit (44 vs. 55%) in bulky Ib (cancer diameter of more than 4cm) and IIa cervical carcinoma if para-aortic lymph nodes are included in the target volume, although there is no difference in disease-free survival nor in the control of local disease between pelvic irradiation and pelvic plus para-aortic irradiation [33]. The reported 10-year survival difference can be explained by a lower incidence of distant failures, eventually with a better salvage in complete responders who later failed locally, or a difference in the death-rate due to treatment-related complications (see late effects). One should be aware that 37% of those patients did not have their para-aortic nodes evaluated surgically or radiologically. The EORTC trial performed on more advanced cervix cancer (comparing pelvic plus para-aortic vs. pelvic volume in early clinical stages with positive LAG or histologically proven pelvic nodes, and LACC, i.e. IIb and III), does not show any benefit in survival, local control or overall distant metastases [14]. There was a clear increase in the incidence of severe digestive complications in patients receiving para-aortic irradiation (9 vs. 4.8%) [14,41]. However, considering the reduced incidence of para-aortic and distant metastases in patients without recurring tumor at pelvic sites, if treated with extended fields, the authors proposed to treat para-aortic nodes where there is a high probability of local control [14]. In the present survey, about 90% of the centers are treating this large volume if they have arguments for positive para-aortic and/or pelvic lymph nodes.

A third important parameter relates to the quality of the brachytherapy. Brachytherapy is an essential component of treatment in LACC, although there is no consensus on the optimal dose-rate. A majority of centers are using LDR. A randomized trial comparing HDR vs. LDR showed similar 5-year survival rates, but a significant difference in favor of LDR as far as toxicity is concerned (10% moderate to severe complications in HDR compared to 4% in LDR) [39]. The question on dose-rate is not definitely settled, with some authors confirming the importance of dose-rate, although at a different level, i.e. comparing two low dose-rate levels [23], and others rejecting the conclusions of the Osaka trial stating that there is no increase in late toxicity [35].

4.2.3. Chemotherapy

The addition of chemotherapy to radiotherapy has become standard in the treatment of LACC [34]. Morris et al. demonstrated in a randomized trial the beneficial effects of adding 5-fluoro-uracil and cisplatinum to radiotherapy in LACC, resulting in a significant improvement in survival (from 73 vs. 58%) [26]. The Gynecologic Oncology Group compared, in a randomized fashion, cisplatin vs. cisplatin plus hydroxyurea, and 5-fluorouracil vs. hydroxyurea alone [32]. Cisplatin containing regimens improve the survival and progression-free survival in LACC [32].

One might expect major changes in treatment prescriptions following these randomized trials. The frequency of adjunctive chemotherapy already changed from 6% in 1984 to 24.8% in 1990. In the patterns of care study, 12% of the patients were treated with concurrent chemotherapy at the cost of a greater morbidity [25,27]. In view of an unproven benefit at that time, it is interesting to note the frequency of use of chemotherapy and especially neoadjuvant chemotherapy. One could wonder why some patients with LACC are still submitted to neoadjuvant chemotherapy, as a sufficient amount of data issued from randomized trials show a deleterious effect on survival [24,30,36,37]. A substantial reduction in survival from 39 to 23% at 5 years has been shown by Souhami et al., comparing radiotherapy to neadjuvant chemotherapy followed by radiotherapy in patients with FIGO stage IIIb [37]. The issue of chemotherapy is not definitely settled and a lot more emphasis will be put on concomitant chemo–radiotherapy, especially after these two positive randomized trials. The advantages are spatial cooperation and additive or supra-additive effects on the primary tumor. For spatial cooperation, one should realize that distant metastases as the first site of failure are rare (5–15%), and that distant metastases are not related to the stage. Regarding the effect on the locoregional control, most of the drugs are used because of their capacity to sensitize cancer cells to ionizing irradiation. Cisplatin is one of the most frequent agents reported to be used, together with radiotherapy, in the present survey. Indeed, clinical experience favors cisplatin as the drug of choice in various human tumors. However, some experimental data in vitro, especially on human cervix cancer cell lines, show that cisplatin leads to additive toxicity and not radiosensitization [4].

4.3. New approaches

Possible factors affecting the outcome in the treatment of LACC are intrinsic radio-resistance, tumor proliferation and hypoxia. Most of the centers of the RCG are willing to participate in trials addressing these issues. The highest rating is obtained for a trial combining chemotherapy as a concomitant sensitizer to radiotherapy, which obviously would require running phase I/II trials if drugs like taxol or gemcitabine have to be used, because the data indicate an increase in gastrointestinal toxicity.

The importance of reducing the overall treatment-time is also considered an important issue in the treatment of LACC. This reflects evidence issued from retrospective studies addressing the importance of the 'time package deal' in LACC [6,11,12,21,28,29,40]. As stated by Eifel 'a comparison between policies that emphasize early intracavitary treatment and short 5–6-week overall treatment-times with those that emphasize an initial course of pelvic treatment to achieve greater tumor regression before brachytherapy would be of considerable interest' [8].

Last but not least, hypoxia is certainly an issue in cervix cancer, as shown by different authors performing in vivo measurements and seeking a correlation between low tumor pO_2 and outcome [16,17]. The hypoxia in cervix tumors provides a physiological selective pressure for the expansion of HPV-infected epithelial variants that have lost their apoptotic potential, which is deemed to be a supplementary reason for radiation resistance [13,19]. The Radiation Therapy Oncology Group tested misonidazole as a hypoxic cell-sensitizer in a randomized trial; no improvement in survival was observed [2]. The Gynecology Oncology Group compared hydroxyurea vs. misonidazole with no improvement in survival [38].The Medical Research Council Working Party on advanced carcinoma of the cervix ran another randomized trial with Ro 03-8799 (pimonidazole) as a hypoxic cell-sensitizer. They observed no benefit by adding pimonidazole to radiotherapy, and a truly adverse effect of the drug was a possible cause of failure in this trial [7]. A new approach is the use of bio-reductive drugs, such as tirapazamine (SR-4233), which in contrast to misonidazole and pimonidazole, offers a selective way of killing those resistant hypoxic cells.

The presence of HPV opens new directions for radiation biology research, as it is currently known that HPV oncoproteins E6 and E7 inhibit both p53 and Rb proteins, both playing an essential role in the cell cycle machinery, and hence, influencing the cell-cycle response to stress [18]. Mechanisms of inhibition of E6 and E7 expression could reinstore p53 functionality and modify radiation response.

5. Conclusions

Several questions are unresolved in cervix cancer. These uncertainties are reflected in the answers provided by the members of the RCG on questions related to staging, treatment options and techniques, and on innovative approaches to be tested within trials. However, a clear shift in patterns of care does occur in cervix cancer treatment. There seems to be a decrease in the number of earlier stages secondary to screening policy, but on the other hand, there is a sufficient number of IIIa and IIIb disease, leaving some space for trials within Europe. Our survey reflects the interest within the RCG to launch and participate in a large prospective multicenter trial in Europe. However, we need an educational program to improve our 'standards' of care, and to adhere to the principles of evidence-based medicine. A comprehensive quality-control program is mandatory, especially due to the complexity of the combination of external irradiation and brachytherapy. As a matter of fact, this program is a prerequisite to launching any kind of trial in LACC.

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