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## Challenges and advances in cervix cancer treatment in elder women

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## Abstract :

With population ageing, cancer treatments in elder patients is becoming a true public health care issue. There is an authentic dilemma between patient's frailty, residual life expectancy and the toll that take anticancer treatments. Since elder patients are almost always excluded from clinical trials, it is hard to get robust scientific data on the tolerability of oncologic treatments and to set in place recommendations.

Cervix cancer is traditionally diagnosed in younger women but it has a 2<sup>nd</sup> incidence peak between 60 and 70 years old. Cervix cancer in elder patients is a subject to many questions in terms of screening and is a therapeutic challenge.

This article reviews literature data on these different aspects, from screening to surgery, from radiotherapy to brachytherapy, from chemotherapy to supportive care, from immunotherapy to geriatric assessment. We tried to show how modern therapeutic innovations may benefit elder patients. Expected benefits in terms of efficacy and toxicity may overcome the long-lasting tendency to undertreatment in elder patients and improve their quality of life after cancer treatment.

In 2020, there seems to be less and less reasons justifying that elder women with cervix cancer may not receive the appropriate treatment.

Keywords : geriatric assessment, cervix cancer, elderly , screening, surgery, radiotherapy, chemotherapy, supportive care, immunotherapy, clinical trials, frailty, toxicity, quality of life

# Introduction

Elder patients represent a large proportion of oncology patients. In the next decade, it is estimated that patients over 65 will represent more than 70% of new diagnosed cancer cases (1).

Despite these numbers, elder patients are underrepresented in clinical trials. And even when they are included in such trials, they do not represent faithfully the general elder population since they are de facto selected on their good performance status and mild comorbidities. This poor data in literature is furthermore complicated to interpret since there is a wide heterogeneity in the definition of "elder patient" : are we old when we are 60 ? 65 ? 70 ? 80 ? (2)

In this review, we chose to address specificities in cervix cancer treatment in elder women. Indeed, this tumor classically considered to be a young women issue actually has a second peak of incidence between 60 and 70 years old, with a constantly rising incidence in this group of patients (3). About 30% of cervix cancers are diagnosed after 65 years old while this age group represents 53% of deaths from cervix cancer (2015 INCa data) (4).

It is striking to acknowledge that specific survival in cervix cancer is substantially lower in elder patients : 38% after 75 years old versus 82% for 15-44 years old (INCa data (4)). This difference may be explained by delayed diagnosis (5) but also by a strong tendency towards undertreatment of older patients, related to psycho-social determinants or beliefs from general public but also sometimes from doctors (6). A National Cancer Database analysis showed that less than one third of patients above 60 yo received standard care and that age was an independent predictive factor towards not receiving appropriate treatment (7). In advanced diseases, 12% of patients above 80 yo won't receive any specific treatment versus less than 4% in patients under 50 yo (8).

There are admittedly treatment refusals from patients and some situations where every treatment is contraindicated for medical reasons, but one ascertains in some series that for most elder patients, the possibility of an oncologic treatment was not even discussed (9).

Thus, it seems essential to update on particularities in cervix cancer treatment in elder patients at every stage of the disease, from diagnosis to life after cancer.

## Diagnosis and prevention

American, European and French recommendations advocate pap-smear screening until 65 yo (10–12). The legitimate question is whether one should extend screening beyond 65 years old since there is a second incidence peak of cervix cancer between 60 and 70 yo, as stated previously.

Against screening extension beyond 65 yo, one can argue that there is less HPV in this population (13), which would increase the number of normal pap-smears (efficiency decrease) and the number of false-positive tests (risk of overtreatment and anxiety, non-negligible risks in that particular population) (14). Furthermore, given natural history of carcinogenesis in cervix cancer (> 10 years), competitive mortality in elder patients decreases their probability of ever developing a malignant disease.

However, it is indisputable that population is aging and that in most developed countries, life expectancy is constantly rising (15). Furthermore, French and American recommendations are certainly in favor of screening until 65 yo but only provided it has been appropriately conducted until this age. And yet screening coverage, traditionally low in France, is even lower in 55-65 yo since it is only 45% (2004-2006 data) (16). The majority of cervix cancers beyond 65 yo occur in women not or incorrectly screened until then, which translates into a mortality rise in this population (17). However, even in patients who had a regular prior gynecological follow-up, it was reported in a large French study that the number of abnormal pap-smears beyond 65 yo remained relatively high, at 14.2 per thousand (18). Recent European publications support screening extension beyond 65 yo based on these data (5,19). Also in favor of screening extension, one knows that persistent HPV infections are more frequent with age (20), thus increasing the risk of developing an invasive disease compared to younger women (in a large series from New-Zealand, among women carrying a CIN3 lesion, only women above 50 had a statistically significant increase of risk of developing an invasive disease, with an Odds Ratio of 2.5 [95 %IC : 1.0–6.7]) (21).

Hence, it seems reasonable to keep on offering cytology in women over 65 yo who ask for it, who have a HPV history (22), who didn't get three consecutive normal pap-smears or those who have a concomitant predisposing disease (immunodepression for instance).

From the age of 30 years to 65 years, the French Haute Autorité de Santé (HAS) recommends in 2019 that the HPV test replace cytology as the primary cervical screening test since it has greater sensitivity for the detection of precancerous lesions and it is more effective in terms of reducing the incidence of precancerous lesions and invasive cancers in women over the age of 30 years (23). Its potential place in patients over 65 remains to be specified but it could be an interesting tool in discriminating patients at risk (24).

As in younger patients, there is a crucial role for an accurate diagnostic imaging to choose the best treatment option in elder patients. A pelvic MRI is necessary to determine tumor size, parametrial involvement, vaginal extension and uterine corpus infiltration. A PET-CT is also useful to evaluate lymph node and metastatic extension (25).

## Comprehensive geriatric assessment (CGA) in geriatric oncology

Frailty is a key concept in geriatric medicine. It reflects a decrease in physiological abilities which alters adaptation mechanisms to stress (26). It is a risk factor for mortality and pejorative events (inabilities, falls, hospital admissions, nursing home admission). Frailty is marked by an age above 85 yo, an abnormal ADL score, the presence of three or more comorbidities or the presence of at least one geriatric syndrome (27).

Knowledge of pre-existing frailty is a key factor in the treatment decision of elder patients.

Pre-therapeutic comprehensive geriatric assessment systematically (CGA) assesses different fields : comorbidities, autonomy, social environment, cognition, nutritional status and medication (28). It categorizes patients into three groups : group 1 being robust patients, independent and without any significant comorbidity ; group 2 being vulnerable patients, presenting with dependence on IADL or 1 to 2 significant comorbidities ; group 3 being fragile patients (27). For robust patients, one would direct the patient preferably towards standard treatment while exclusive supportive care would be preferred for fragile patients. An adapted treatment should be offered to vulnerable patients. Two studies showed that geriatric assessment changes the initially made therapeutic proposition in one third of cases, mostly when ADL score is abnormal or in cases of denutrition (29,30). This shows the utmost importance of a multidisciplinary evaluation in order to choose the best therapeutic option in elder patients.

Furthermore, in identifying previously undetected health issues, geriatric assessment allows for corrective geriatric interventions that may limit the risk of geriatric complications during treatment and sustain the independence of the patient (nutrition intervention, adaptation of home help, adaptation of prescriptions to limit drug interactions, fall prevention) (31,32).

However, not all patients beyond 70 yo will benefit from comprehensive geriatric assessment in oncology. With this in mind, the G8-Oncodage questionnaire is a simple tool (takes less than minutes to fill) that was developed for oncologists and surgeons (33). A G8 score  $\leq 14$  is associated with an abnormal CGA with a 76.6% sensitivity and a 64.4% specificity. This score was updated recently (34). An abnormal score should lead the oncologist to refer the patient for CGA.

## Early stage cancer : place of surgery

Several retrospective studies seem to indicate that surgery is feasible in elder women (35,36). However, frequent comorbidities and frailty in this population bring a legitimate concern towards surgery's morbidity in elder patients. Indeed, an American database study showed that post-operative complications were systematically increasing with age in 8200 patients treated with open hysterectomy between 1998 and 2010 (37). There were also return home issues in 12.3% of women over 70 yo (versus 0.5% of women under 50). Peri-operative mortality in these patients was also 30 times higher than patients under 50 ( $p < 0.0001$ ). There is still a reticence to operate on these elder patients despite surgical technique and supportive care improvements that, one can suppose, have improved outcomes since that time. Indeed, in the review from Wright et al., only 16% of patients over 70 had a surgery versus 54% in younger patients ( $p < 0.0001$ ) (8).

Numerous retrospective studies have shown the benefit of mini-invasive surgery in cervix cancer in terms of reduction of post-operative complications (38,39). That's how these techniques have naturally become routine care and were recommended by NCCN and ESGO until 2018 (40,41). However, LACC study challenges this paradigm by reporting an inferior disease-free survival at 4.5 years in the laparoscopic / robotic surgery arm versus open surgery arm (86% versus 96.5% respectively) (42). This inferiority was confirmed in terms of overall survival (3-year survival of 93.8% versus 99% respectively, HR = 6; 95% CI [1.77 - 20.3]. The LACC trial results

have triggered many debates and controversies in scientific communities, especially criticizing the methods and exportability of the trial's results. One knows that open surgery bears a higher morbidity than the laparoscopic approach, especially in elder patients. Thus, in elder women, it may be reasonable to maintain the laparoscopic approach in order to reduce morbidity. These results have been confirmed by several studies after the publication of the LACC trial, placing laparotomy as the standard surgical approach for many guidelines and teams. However, one paper reported good survival outcomes with a combined laparoscopic and vaginal approach with primary closure of the vagina (43) ; and in the LACC trial as in other studies, elderly women were only a minority. In this specific population the benefit / risk ratio should be evaluated for each patient balancing the risk of MIS versus the risk of postoperative complication and morbidity related to laparotomy. Comorbidities, such as obesity, diabetes, cardiovascular disease, anticoagulation therapy, etc. should be taken into account, as well as the advice of onco-geriatricians.

Nodal staging is also a matter of importance in localized cervix cancer. Even if the procedure has not made it to recommendations yet, sentinel node biopsy seems to give good results in terms of sensitivity and negative predictive value (92% and 98% respectively in SENTICOL study, on IA1 tumors with lymphovascular space invasion up to IB1 stages) (44). SNB reduces morbidity (lymphedema, lymphocele, vascular complications etc.) and thus could be particularly interesting in elder patients. Results of SENTICOL III trial on 3-year survival are awaited to confirm the equivalence of SNB to traditional lymph node dissection in this strategy of therapeutic de-escalation (45).

Strategies of conservative surgery have essentially been developed in a fertility preservation context (46). Such techniques are supported by several retrospective studies (47,48). Some authors suggest that since they reduce urinary and digestive toxicity, they may also benefit elder patients (49). If the ongoing SHAPE trial shows non-inferiority of simple hysterectomy compared with radical hysterectomy (+ lymph node dissection) in localized cervix cancer (IA2 to IB1 FIGO 2009), it could reinforce further this strategy.

An acceptable alternative for non-surgical patients (recused by the anesthesiologist or inoperable cases) in localized cancers is an exclusive radiotherapy, as validated in Landoni et al.'s randomized trial, recently actualized with a 20-year follow-up (50). It showed an identical overall survival at 20 years between the two



groups (72% in surgery group and 77% in radiotherapy group,  $p=0.28$ ), with significantly less complications in radiotherapy arm (32% versus 23%,  $p=0.006$ ).

## Locally advanced disease

Standard care for locally advanced cervix cancer relies on radiochemotherapy followed by an utero-vaginal brachytherapy (51). This strategy entails several challenges when it comes to elder patients, at each step of the treatment.

### *Para-aortic lymph node dissection*

Compared to younger patients, elder patients tend to have less frequently a complete nodal staging (52). The benefit-risk balance should indeed be carefully weighted in elder patients due to the expected morbidity of the nodal staging. Elder patients, due to heavier cardiovascular and respiratory comorbidities may have a hard time maintaining Trendelenburg position, though necessary for a laparoscopic or a robotic approach (53). And yet, laparotomy gives more urinary and vascular complications (52). Moreover, one knows that when atheromatosis is present, which is frequent in elder patients, vascular complications of lymph node dissection are even more frequent.

In a high surgical risk patient, a reasonable attitude could be to avoid lymph node dissection when PET-CT is negative in the pelvic area since the false-negative rate in the para-aortic area is 9% in that case. However, if PET-CT shows hypermetabolic nodes inside the pelvis, the risk of false-negative is much higher, around 22% (54).

If LND is not feasible, prophylactic para-aortic irradiation does not seem to be legitimate since it adds a great deal of morbidity to pelvic irradiation, especially in terms of digestive toxicity, while it has shown no efficacy in this context (55). A possible alternative attitude is to adapt irradiation field according to a nodal risk stratification strategy, as suggested by EMBRACE II international trial (56). The latter stipulates a prophylactic

irradiation up to L2 for « high nodal risk patients » (being patients with at least one common iliac pathological node or at least 3 pelvic nodes).

To sum up, the indication of para-aortic lymph node dissection in elder patients should be a case-by-case assessment in a multidisciplinary board, taking into account all previously mentioned elements.

### *Concomitant chemotherapy*

Several randomized trials have shown a benefit to adjunction of chemotherapy to radiotherapy in locally advanced cervix cancer. Cochrane 2010 meta-analysis confirmed this benefit, with a DFS gain of 8% and an OS gain of 6% at 5 years (57). Platinum-based and non-platinum-based regimens were shown to be efficient with no superiority of a regimen over another, but the most commonly used molecule in routine practice is Cisplatin 40mg/m<sup>2</sup> administered weekly. Of note, the majority of patients included in these trials were under 65 years old.

In elder women, there are specificities regarding expected chemotherapy tolerance. There are some uncertainties in pharmacodynamics because of the frequent hypoalbuminemia, renal function alterations and modified repartition between lean body mass / body fat.

Classical side effects of platinum-based regimens may reinforce some geriatric preexisting syndromes : hearing loss, inferior limb neuropathy (risk of falls), extremity paresthesia (difficulties in dressing, writing, preparing meals), fatigue (loss of autonomy), vomiting / diarrhea (dehydration risk), nausea and anorexia (Fig. 1). One also needs to take into account social isolation and pre-existing cognitive impairment that may compromise the appropriate management of chemotherapy toxicities (if for example the patient is not capable of alerting someone in case of febrile aplasia or bleeding) (58).

Cisplatin-induced nephrotoxicity is correlated with age, in particular when some other nephrotoxic medication is associated (non-steroid anti-inflammatory, angiotensin converting enzyme inhibitors etc.) (59). Given these pitfalls with Cisplatin, weekly Carboplatin AUC2 is often chosen in the elder population for its better tolerance, especially when the patient is frail or has an altered renal function (60). Since the meta-analysis has not shown

an inferiority of this regimen, this option seems perfectly acceptable if Cisplatin seems unreasonable but the patient is still fit for chemotherapy. However, its greater potential for thrombocytopenia deserves a close follow-up, especially since radiotherapy will diminish an already limited medullar reserve in an elder woman. The benefit-risk balance must be carefully weighted in patients under anticoagulants / platelet antiaggregants or in patients with a high risk of fall.

The CRASH score includes various oncologic and geriatric characteristics of the patient and allows for a priori risk estimation of chemotherapy-induced severe hematological and non-hematological toxicities. It is an interesting tool available to the oncologist to choose a potential concomitant treatment (61).

If all chemotherapy regimens are contra-indicated, exclusive radiotherapy remains a valid therapeutic option (62).

### *Radiotherapy*

Current recommendations for locally advanced cervix cancer advocate a pelvic irradiation +/- para-aortic irradiation at 45-50.4 Gy in 25 - 28 fractions of 1.8 – 2 Gy with a concomitant or sequential boost on pathological nodes up to 60 Gy EQD2 (Equivalent Dose in 2 Gy fractions) (including brachytherapy dose contribution) (63). This irradiation should be followed, whenever technically possible, with utero-vaginal brachytherapy to escalate the dose on the cervix to 85 - 90 Gy EQD2.

The tolerance of this therapeutic sequence is sometimes difficult in elder patients. As for chemotherapy, side effects of radiotherapy tend to favor the decompensation of pre-existing frailties (Figure 2) : diarrhea / vomiting and dehydration, anorexia and sarcopenia, anemia and fatigue (64), lower limbs lymphoedema and walking ability disorders (55), oosteoporosis and sacral « H-shaped » fracture (65)... .These pitfalls may be responsible for treatment interruptions or overall treatment time prolongation (3% and 29% of patients respectively in Lindegaard et al. series) (66). Possible ways to improve tolerance from the radiation oncologist's point of view are numerous : volume reduction, precision improvement, dose reduction, dose gradient increase, hypofractionnation, overall treatment time shortening etc.

The last decades have been characterized by some major evolutions in terms of radiotherapy techniques, especially Intensity Modulated Radiation Therapy (IMRT), that has shown its benefit in terms of dose reduction to bowel and rectum in cervix cancer treatment, without any difference in overall survival (67). It also makes bone-marrow sparing possible, as one knows that 50% of it is located inside pelvic bones (68). Intensity modulation, widely adopted in clinical routine at present time, seems particularly interesting for elder patients in its ability to reduce toxicities (69). The counterpart in terms of session time prolongation seems acceptable (20 minutes versus 10 minutes for a 3D conventional session).

Appropriate bladder filling and rectum emptying for each session, aiming at reducing dose received to the posterior bladder wall and the anterior rectal wall, may be difficult to achieve in elder women (urinary incontinence, constipation tendency, troubles in understanding instructions) and this deserves to be anticipated at simulation CT. A continuous follow-up during treatment with radiation oncologists and radiation therapists may prove itself particularly useful (reminder of preparation instructions, lifestyle and dietary advice etc) (70).

Even if volume reduction is prone to reduce toxicity, it seems unacceptable to omit some of the recommended volumes in elder patients (71). However, Image Guided RadioTherapy (IGRT) with a cross-sectional imaging modality (Cone Beam CT CBCT) allows for daily repositioning taking into account cervix and uterine movements and thus allows for Planning Target Volume (PTV) margins reduction (56,71).

Para-aortic prophylactic irradiation should not be systematically applied as discussed before, even when lymph node dissection was not performed. However, para-aortic irradiation with a boost on pathological nodes remains essential if PET-CT is positive in the para-aortic area. The tolerance of such an irradiation, already poor in younger women, is particularly difficult in elder women due to digestive disorders that may require aggressive symptomatic treatment or even hospitalization if dehydration occurs. Sometimes a close follow-up from the geriatrics team is necessary during treatment, in an ambulatory mode or in hospitalization.

In terms of dose, it has been shown that limiting the dose delivered to pelvis at 45 Gy allowed for an increase in local control while allowing more leeway for brachytherapy which is the best modality for dose escalation on

central pelvis (72). Delivering 45 Gy to the pelvis instead of 50.4 Gy also helps reduce toxicity, even in elder patients.

Hypofractionated schedules, while reducing overall treatment time, improve patient's comfort and thus compliance. They are often chosen in many tumor types in elder patients, at the cost of a higher long-term morbidity compared to conventional fractionations, especially in cervix cancer, hence the reluctance in using such fractionations with a radical aim (73). However, that risk must be weighted with the patient's life expectancy.

Conventional fractionations remain thus standard in cervix cancer but IMRT allows for an "integrated boost" (meaning that the dose complement on involved nodes is delivered concomitantly with pelvic irradiation) which has an advantage in reducing overall treatment time.

In cases of very altered general condition with a life span threatened in the short-term, a hypofractionated hemostatic or antalgic irradiation may be carried out (74).

### *Brachytherapy*

In the US, the uprising of modern radiotherapy techniques such as IMRT and stereotactic radiotherapy have led to a proportional decline in the use of gynecologic brachytherapy and, with it, to a proportional decline in the prognosis of cervix cancer (HR for death = 1.86 ( $p < 0.01$ ), National Cancer Database) (74). One recognizes that one of the strongest factors associated with the non-use of brachytherapy in multivariate analysis was age ! Even in Gynecologic Oncological Group (GOG) clinical trials, the rate of is as high as 30% in patients over 70 versus 13% in patients under 40 (75). And yet, in published studies where brachytherapy is performed, local control is identical in all age groups, and in particular above 65 (76). Tolerance and efficacy of brachytherapy were improved due to technical evolutions over the years. Withdrawal from the market of Iridium wires in 2014 has led brachytherapy units to adapt their practice towards source projectors. They carry some particular assets in terms of tolerance for elder patients. Although pulsed dose rate treatment confines the patient to bed for 48 to 72 hours, interpulse time and better caregivers' radioprotection offers much more nursing possibilities than iridium wires, to avoid decubitus complications and failure to thrive syndrome. On the other hand, high dose rate has the advantage of being an ambulatory treatment, and thus also reduces the risk of

decubitus complications, but has the disadvantage of potentially requiring multiple implants and thus several anesthesia (general or spinal).

This evolution towards source projector also allows dosimetric optimization to escalate the dose inside the cervix and residual tumor at time of brachytherapy (HR CTV) while protecting at best adjacent Organs At Risk (OAR) (77).

The uprising of image guided brachytherapy, so-called 3D because leaning on cross-sectional imaging (ideally an MRI), has marked the entrance into modern brachytherapy. It is defined by an adaptive definition of tumor volumes (HR and IR CTV) (78,79) and thus a better dosimetric optimization (80). A prospective French study comparing results of 2D versus 3D image guided brachytherapy reported a significant improvement in local relapse free survival (78.5% versus 74%,  $p=0.003$ ) and a reduction of grade 3-4 toxicities (23% versus 3%,  $p=0.002$ ) (81). By reducing morbidity, these technical evolutions in brachytherapy seem particularly interesting in elder frail patients.

Furthermore, the adjunction of an interstitial component to conventional intracavitary implant improves dose coverage especially for the tumors that remain quite large at time of brachytherapy but also, because of a better conformity, reduces the dose to OAR. (RETROEMBRACE study data) (82). In practice, this kind of implant is utterly feasible in elder patients since it prolongs operating time of only 30 minutes. Many IRM-compatible commercial applicators allow for para-vaginal and / or parametrial interstitial implant in a simple and reproducible way in routine. A morphine titration is sometimes necessary after that kind of implant but global tolerance is remarkably good.

Despite technical progress and good results in terms of quality of life, a meta-analysis of 24 publications about cervix cancer in elder patients shows that in some studies, brachytherapy was not used by fear of toxicity (2). In Mitchell et al. study, the proportion of patients who did not undergo brachytherapy was as high as 11%, 20% and 40% in the 60-69, 70-79 and 80-89 yo groups respectively(83). The reasons cited were technical ones (49%), comorbidities (69%) and patient's refusal (38%) (84). The reasons of unfeasibility are mostly the absence of vaginal delivery and tumor size (85) even if tandem insertion difficulties are less and less frequent in modern

brachytherapy thanks to per-operative ultrasound guidance (86). Patients having a formal prohibition to any anesthesia may benefit from an implant under exclusive premedication (87).

Though perceived “aggressive”, brachytherapy is actually rather well tolerated in most of the elder patients. Published series account for an excellent local control (91% at 3 years) with low toxicity and a mild impact on long-term quality of life (76). Gustave Roussy’s experience shows that brachytherapy is feasible in this population (98.2% of treatment completion) with no decrease of efficacy with age (specific survival at 3 years of 89%) and with acceptable toxicity (88).

### *Adjuvant chemotherapy*

While waiting for OUTBACK trial results (89), there is no standard of care as regards adjuvant chemotherapy. However, 3 to 4 cycles of adjuvant platinum and taxane based chemotherapy is regularly proposed by oncologists in high risk tumors, in particular for patients that had an initial para-aortic involvement.

In elder patients, and considering the absence of proof of benefit of such an adjuvant chemotherapy, cautiousness is warranted. The feasibility of such chemotherapy needs anyhow to be reevaluated at the end of radiochemotherapy – brachytherapy sequence depending on the general condition of the patient.

### *Synthesis on locally advanced cervix cancer in elder patients*

In the end, therapeutic sequence in locally advanced cervix cancer in elder women, although tough, seems feasible. Retrospective studies report an obviously lower overall survival but an identical specific survival compared to younger women, around 81% at 3 years, without additional toxicity (90–92). Even in patients bearing heavy comorbidities, completeness of the treatment seemed to improve overall survival at 5 years in a large American database : 46.6% vs 36.0% for 61 – 70 yo, 51.4 vs 25.9% for 71-80 yo and 26.3% vs 11.2 for patients over 80 yo ( $p < 0.001$ ). Physiologic age must be considered firstly over chronological age in therapeutic decisions.

## Metastatic stage

### *Oligometastases / oligoprogression*

Stereotactic irradiation of limited metastatic disease is a pioneering strategy initially developed in colorectal and lung cancers. In an oligometastatic or oligorecurrent context, stereotactic radiotherapy may be incorporated in a “radical” approach when performed on all metastatic sites +/- associated with local radical treatment. It may also be a therapeutic sparing strategy in oligoprogression situations. Some encouraging data are available concerning this strategy in cervix cancer (Figure 2) (93). Hence one can immediately imagine what benefits elder patients might draw from it, since it is little morbid, highly efficient and it has the potential to avoid or delay systemic treatment (94). It seems also particularly competitive compared with metastasectomy in terms of acceptability, especially in elder patients.

### *Chemotherapy*

Standard first-line chemotherapy relies on a Cisplatin – Paclitaxel association, that showed its superiority in PFS compared with Cisplatin monotherapy, but with no gain in OS (95). Carboplatin is often preferred in elder patients for tolerance reasons, as mentioned above, and is supported by the Japanese study JCOG0505 showing lack of inferiority of Carboplatin compared to Cisplatin (96).

Risk – benefit ratio of this palliative chemotherapy needs to be carefully weighted in elder women because of its toxicity (20% of grade 3+ vomiting, 13% of febrile neutropenia in Monk et al. study) and its non-negligible impact on quality of life. Doses may be adapted on a case by case basis but systematic dose reduction is not recommended (97).

In cases of geriatric frailty, a monochemotherapy regimen should be put forward.



## *Immunotherapy*

Checkpoint inhibitors have revolutionized standard of care in many cancer types over last years but results in cervix cancer remain limited at the time. A phase II study presented at 2019 ASCO evaluating Pembrolizumab in 2<sup>nd</sup> line and further showed a response rate of 12% and an OS of 9.4 months. Several phase III trials are currently running in the first line setting or in locally advanced stages, such as MK-3475 and ATEZOLACC. FDA just approved their use in metastatic stages.

In elder patients, it is classically admitted that their immune system is less effective (98). However, PD-1 / PDL-1 inhibitors are usually well tolerated (as well as younger patients) and **are widely prescribed in routine practice for lung or bladder cancers to patients who are unfit for chemotherapy. could in the future represent a good option for elder patients.**

## *Clinical trials*

Elder patients are almost systematically excluded from clinical trials and very few studies are specifically dedicated to them. For example in the US, patients over 65 represent 36% of major trials' inclusion while they represent 60% of the population (2004 data) (99).

In locally advanced cervix cancer, it is interesting to note that the international EMBRACE II trial has no limit of age in its inclusion criteria (56). Including our patients in this protocol may finally provide some good quality data of efficacy and tolerability of a standard approach in elder patients.

Classical endpoints in clinical trials, being OS and PFS, are most likely unsuitable to evaluate elder patients. Thus specific survival, handicap free survival, toxicity and quality of life are probably better surrogates of a good quality treatment in a geriatric population (100).

## Conclusion

Standards of care in cervix cancer schematically rely on surgery for localized stages, on radiochemotherapy followed by brachytherapy for locally advanced stages and on chemotherapy for metastatic stages. Treatments are getting more and more efficient and safe, in conjunction with evolutions in systemic treatments, surgery and radiotherapy techniques (Figure 2). Given the therapeutic advances and good functional results, there seems to be less and less reasons in 2020 to deny our elder patients standard care. It is of utmost importance to personalize treatments depending on pre-existing geriatric frailties. Geriatric oncologists are a partner of choice in this approach. Reliable data coming from clinical trials that include the geriatric oncology population are still cruelly lacking.

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