# Toxicity of concurrent chemoradiotherapy for locally advanced cervical cancer

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**Summary**

*Aim of the study:* The analysis of acute and late toxicity of concurrent chemoradiotherapy (CCRT) for locally advanced cervical cancer (LACC) based on review of 120 patients treated in Centre of Oncology in Krakow between 2001 and 2007. *Materials and Methods:* Medium age of the patients was 52 years (43-66). Overall, 12 patients (10.0%) were in Stage IB2, 54 (45.0%) in Stage II, 43 (35.8%) in Stage III, and 11 (9.2%) in Stage IVA. Squamous cell carcinoma was present in 114 (95.0%) patients. Well-differentiated (grade 1) tumour was found in 39 (32.5%) patients, moderately differentiated (grade 2) in 41 (34.2%), and poorly differentiated (grade 3) in 40 (33.3%). Karnofsky performance status score was 70 in 72 (60.0%) patients, and 80-90 in 48 (40%). External radiation therapy was delivered with high-energy six to 15 MV photon beams using four-field brick technique. The total dose of 50 Gy was given in 25 fractions within five weeks using standard fractionation. Concurrently with external radiotherapy, six cycles of chemotherapy were administered to all the patients as an intravenous infusion of once-weekly cisplatin 40 mg/m$^2$. On completion of external beam radiotherapy, low-dose rate brachytherapy with tandem and two colpostats was performed to deliver the dose of 40 Gy to point A in two 20 Gy insertions at weekly intervals. *Results:* Of the 120 patients in the investigated group, 78 (65%) were disease-free for five years. Symptoms of acute treatment-related toxicity grade 3 or 4 (WHO) occurred in 21.6% of patients including leucopoenia in 7.5%, anaemia in 5.0%, nausea and vomiting in 3.3%, diarrhea in 5.0%, and urinary tract infection in 0.8%. Full planned treatment (teleradiotherapy + chemotherapy + brachytherapy) completed 78.3% of the group; full planned radiotherapy without full chemotherapy completed 20% of the patients. Late treatment complications of grade 3 or 4 were observed in two (1.6%) patients (narrowing of large intestine requiring surgery and recto-vaginal fistula). *Conclusions:* In patients with LACC treated with CCRT, the most frequent acute toxic effects include: haematological disorders (leucopoenia, anaemia), gastrointestinal disorders (nausea and vomiting, diarrhea), vulvo-vaginal disorders, and urinary tract infection. The most frequent late toxic effects included: rectal bleeding, bowel complications requiring surgery, stenosis or recto–vaginal fistula, and haematuria.

*Key words:* Locally advanced cervical carcinoma; Chemoradiotherapy; Toxicity.

## Introduction

Concurrent chemoradiotherapy (CCRT) is nowadays the standard treatment for patients with locally advanced cervical carcinoma (LACC) [1-13]. The introduction of CCRT for the radical treatment of LACC resulted in an improvement in local control, progression-free survival, and overall survival [14-23]. A systematic review by the Meta-Analysis Group, Medical Research Council Clinical Trials Unit (London), of individual patient data from 13 randomized trials showed a six-percent increase in five-year survival with chemoradiotherapy versus the same radiotherapy alone [24]. Vale *et al.* presented a Royal College Radiologists audit of patients treated with radiotherapy in 42 UK cancer centres in 2001-2002. Overall, five-year survival with radiotherapy and chemoradiotherapy was 44% and 55%, respectively. For women treated with radiotherapy, overall survival at five years was 59% (Stage IB), 44% (Stage IIB) and 24% (Stage IIIB); for those treated with chemoradiotherapy, it was 65%, 61%, and 44%, respectively [21]. Although the survival gains are significant, there is concern about the acute and late toxicity of CCRT [24-30]. The audit by Vale *et al.* showed that the addition of chemotherapy to radiotherapy had improved survival compared with radiotherapy alone without an apparent rise in late treatment complications [21]. Some authors conclude that in view of the consistency and extent of the survival benefit for CCRT, the additional acute toxicity appears to be acceptable [3, 7, 8, 10, 23]. Most of the authors consider that serious morbidity is higher in patients treated with CCRT than in those treated with radiotherapy alone [3, 5, 8, 10, 20, 22, 27, 28]. The study by Tan and Zahra has shown that the addition of chemotherapy to radiotherapy for cervical cancer probably improves the survival of patients treated outside research settings, but the benefit may not be as large as that obtained in clinical trials and the risk of serious late toxicity is increased [22]. In the authors' opinion of Klopp and Eifel, the success of CCRT in cervical cancer patients has been limited in part because the side-effects of standard platinum–based chemoradiation regimens already approach the limits of tolerability [14]. Aim

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of this study was to analyse the acute and late toxicity of CCRT in patients with LACC, based on review of the authors' clinical material and as well as literature data.

## Materials and Methods

Between January 2001 and June 2007, 120 LACC patients in Stage IB2-IVA were treated with CCRT at the Centre of Oncology in Krakow. Patients were staged according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system [31]. Two toxicity grading systems for reporting complications of treatment were used: Franco Italian glossary [32] and the National Cancer Institute / Common Toxicity Criteria (1988) (NCI, CTC) [33, 34]. The first one describes toxicity associated with radiation therapy and the second is an elaboration by the World Health Organisation (WHO) for reporting chemotherapy toxicity. Study group patients were chosen using the following inclusion criteria: FIGO Stage IB2-IVA, serum haemoglobin levels > 10 g/dl, white blood cell count > 3,000/µl, platelet count 100,000/µl, and normal renal and hepatic function. Median age of the patients was 52 (range: 43 to 66 years). Overall, 12 patients (10.0%) were in Stage IB2, six (5.0%) in IIA, 48 (40.0%) in IIB, four (3.3%) in IIIA, 39 (32.5%) in IIIB, and 11 (9.2%) in IVA. Squamous cell carcinoma was present in 114 (95.0%) patients whereas adenocarcinoma was observed only in six (5.0%) patients. Well-differentiated (grade 1) tumour was found in 39 (32.5%) patients, moderately differentiated (grade 2) in 41 (34.2%), and poorly differentiated (grade 3) in 40 (33.3%). Karnofsky performance status (KPS) score was 70 in 72 (60.0%) patients, and 80-90 in 48 (40%). Fifty-two (43.3%) patients had haemoglobin level < 12 g/dl before starting CCRT, 16 of whom received pre-treatment blood transfusions.

External radiation therapy was delivered with high-energy six- to 15-MV photon beams using four-field brick technique (anterior, posterior, left, and right lateral fields). Irradiated volume included whole pelvis. The following field borders were used: superior - sacral promontory; inferior - inferior edge of obturator foramina; lateral - one cm off pelvic sidewall; anterior - centre of symphysis pubis; and posterior - lower border of S2 vertebra. Before starting radiotherapy, conventional planning based on orthogonal films was performed for 50 patients and three-dimensional virtual computed tomography (CT) simulation for 70, in order to define target volume and organs at risk (rectum, bladder, and femoral head). The total dose of 50 Gy was given in 25 fractions within five weeks using standard fractionation. Concurrently with external radiotherapy, six cycles of chemotherapy were administered to the patients as an intravenous infusion of once-weekly cisplatin 40 mg/m$^2$. On completion of external beam radiotherapy, low-dose rate brachytherapy with tandem and two colpostats to deliver the dose of 40 Gy to point A in two 20 Gy insertions at weekly intervals. After the treatment, patients were followed-up every three to six weeks and subsequently every three months for five years. In case of clinical suspicion of recurrence, additional investigation included biopsy, magnetic resonance imaging (MRI) or CT scan. Median follow-up was seven years. Survival time was counted starting from the first day of radiotherapy.

## Results

The fate of patients in the investigated group is presented in Table 1. Of the 120 patients in the investigated group, 78 (65%) were disease-free for five years. One patient died of cerebral haemorrhage with no evidence of recurrent disease in the third year after treatment; the second died due to acute sepsis and recto-vaginal fistula occurrence. In 40 (33.4%) patients, the cause of death was uncured cervical cancer. The primary cause of chemoradiotherapy failure in the investigated group of patients was pelvic recurrence, which amounted to 77.5% (31 patients) of treatment failures. Thirteen, i.e. 32.5% of uncured patients, developed distant metastases in lungs (six patients), bones (three patients), liver (three patients), and brain (one patient); in nine (22.5%) cases, it was the only cause of treatment failure.

Table 1 – *The fate of 120 patients in the investigated group.*

| Fate of patients | Number of patients | % |
|---|---|---|
| Survived five years disease-free (five years NED) | 78 | 65.0 |
| Died of other causes | 2 | 1.6 |
| Died of cervical cancer: | | |
| - pelvic recurrence | 27 | 22.5 |
| - pelvic recurrence+distant metastases | 4 | 3.4 |
| - distant metastases | 9 | 7.5 |
| Total | 120 | 100.0 |

Table 2 – *Acute treatment-related toxicity in the investigated group of patients.*

| Acute toxicity | Toxicity grade (WHO) | |
|---|---|---|
| | 1 or 2 | 3 or 4 |
| Haematological toxicity: | | |
| - leucopenia | 52.5% | 7.5% |
| - anaemia | 22.5% | 5.0% |
| - thrombocytopenia | 11.7% | 0.0% |
| Nausea and vomiting | 16.7% | 3.3% |
| Diarrhea | 55.0% | 5.0% |
| Urinary tract infection | 10.8% | 0.8% |
| Acute vaginal mucositis | 1.7% | 0.0% |

*Acute and late toxicity*

Symptoms of acute treatment-related toxicity occurred in 112 (93.3%) patients of the study group, as shown in Table 2. Seventy-two (60%) patients developed leucopenia, in 63 (52.5%) of whom of grade 1 or 2, and in nine (7.5%) of grade 3. Anaemia occurred in 33 (27.5%) patients, including 27 (22.5%) cases of grade 1 or 2, four (3.3%) of grade 3, and two (1.7%) of grade 4. Thrombocytopenia of grade 1 or 2 occurred in 14 (11.7%) patients. In total, acute haematological toxicity was observed in 84 (70%) patients with 74 cases of grade 1 or 2 and ten of grade 3 or 4. Among these patients, 56 developed one type of haematological toxicity and 28 two or three types.

Depending on severity of haematological complications, patients were managed with typical procedures including transfusions, administration of erythropoietin derivatives, haemopoietic agents, etc.

Table 3 – *Course of treatment of 120 patients in the investigated group.*

| Course of treatment | Number of patients | % |
|---|---|---|
| Full-planned treatment completed (teleradiotherapy – brachytherapy - chemotherapy) | 94 | 78.3 |
| Full-planned radiotherapy completed without completing full chemotherapy | 24 | 20.0 |
| Full-planned chemo- and brachytherapy completed without completing full teleradiotherapy | 2 | 1.7 |
| Total | 120 | 100.0 |

Table 4 – *Late treatment complications in the investigated group.*

| Complications | Number of patients | % |
|---|---|---|
| Late complications of grade 1 or 2: | | |
| - persistent diarrhea | 8 | 6.7 |
| - rectal bleeding | 3 | 2.5 |
| - chronic cystitis | 3 | 2.5 |
| - vagina narrowing | 2 | 1.7 |
| Late complications of grade 3 or 4: narrowing of large intestine | | |
| - requiring surgery | 1 | 0.8 |
| - recto-vaginal fistula | 1 | 0.8 |
| No late complications | 102 | 85.0 |
| Total | 120 | 100.0 |

Nausea and vomiting occurred in 24 (20%) cases, 20 (16.7%) of which were of grade 1 or 2, and four (3.3%) of grade 3 or 4. Patients were given typical antiemetic agents including ondansetron and thiethylperazine.

Diarrhoea occurred in 72 (60%) patients; 66 (55%) cases were of grade 1 or 2, and six (5%) of grade 3 or 4. Dietotherapy and typical antidiarrheal drugs were advised; in six cases, severity of rectal reaction was the cause of bleeding.

Urinary tract infection, manifested by pollakiuria, burning sensation, and pain with urination, and even modest haematuria in one case, was observed in 14 (11.6%) patients; treatment-related toxicity was graded 1 or 2 in 13 (10.8%) patients, and 3 in one case.

Two (1.7%) patients developed acute vaginal mucositis of grade 2 toxicity accompanied by slight bleeding from genital tract.

Course of treatment of 120 patients in the investigated group is presented in Table 3. Full-planned treatment was completed in 94 (78.3%) patients of the investigated group.

Twenty-four patients, i.e. 20% of the group, completed full-planned radiotherapy, but were given only three or four cycles of cisplatin. Reduced number of chemotherapy cycles was caused by acute haematological toxicity (ten patients), gastrointestinal disorders of grade 3 or 4 (six patients), disease progression (two patients), significant deterioration of patient performance status with exacerbation of accompanying diseases, such as bronchial asthma, diabetes (four patients), further chemotherapy refusal (two patients).

Full planned radiotherapy (tele- + brachytherapy) was delivered to 118 patients, i.e. 98.3% of the investigated group, 114 (95%) of whom completed the treatment without any interruptions within expected time, and four (3.3%) with one- to two-week break in external beam radiotherapy caused by excessive postradiation reaction in pelvis minor.

In two cases, i.e. 1.7% of the patients, teleradiotherapy was discontinued after delivering 40 Gy due to intensified symptoms of intestine postradiation reaction (bothersome diarrhea). The two patients were given five cycles of cisplatin and four weeks after teleradiotherapy termination when gastrointestinal reaction abated, full-planned brachytherapy was performed.

Late treatment complications (occurring three months after treatment completion or later) were observed in 18 (15%) patients, including 16 (13.3%) cases of mild complications (grade 1 or 2) and two (1.7%) severe (grade 3 or 4). Table 4 presents late treatment complications observed.

Data presented in Table 4 show that the most frequent late complications of grades 1 or 2 occurring in the investigated group were postradiation changes in large intestine and rectum manifested in persistent diarrhea and bleeding. These symptoms were reported in 11 patients (9.2%) and amounted to over two-thirds of all grade 1 or 2 complications. Three patients (2.5%) developed chronic cystitis and two (1.7%) vagina narrowing.

All of the complications were managed with conservative treatment and, in the majority of cases, the symptoms subsided within few months or were considerably reduced (e.g. vagina narrowing).

Severe (grade 3 or 4) late complications were observed in two patients (1.6%) of the investigated group. In one case, it was narrowing of large intestine requiring surgery, which occurred in the 16$^{th}$ month after the treatment; resection of the narrowed section restored normal intestinal passage. The patient survived three years with no evidence of disease. One patient developed recto-vaginal fistula while local disease progression continued (initially in stage IVA). The patient died showing symptoms of acute sepsis.

## Discussion

Of the 120 patients treated in Centre of Oncology in Krakow, five-year NED was recorded in 78 (65.5%) cases, including 83.3% (55/66) of patients in FIGO Stage IB2 - II, 48.8% (21/43) in Stage III, and 18.2% (2/11) in Stage IVA. The results are generally in line with the literature reports in which long-term survival [4-8 years] of chemoradiotherapy patients in study groups of similar clinical profile varies between 47% and 83% with the range of 70-

80% for Stage IB-II, 50-60% for Stage III, and 15-25% for Stage IVA [1, 3, 15, 20-23, 35-47].

*Acute toxicity*

In 112 of 120 patients, i.e. in 93.3% of the investigated group, acute treatment-related toxicity occurred; 14 (11.6%) of the cases were assigned grade 3 or 4, and the remaining 98 (81.7%) grade 1 or 2. The most frequent was haematological toxicity (84 patients, i.e. 70.0%), manifested particularly often with leucopenia, less frequently with anaemia, and significantly rarer with thrombocytopenia. Acute gastrointestinal complications (nausea, vomiting, and diarrhoea) were observed in 72 (60%) patients with only six (5%) cases of grade 3 or 4 toxicity. Additionally, patients in the investigated group developed urinary tract infection and acute vaginal mucositis, their severity, however, was graded only 1 or 2.

Ninety-four (78.3%) of the patients completed full planned chemoradiotherapy. Twenty-four (20%) completed full-planned radiotherapy without completing full chemotherapy, with three or four cycles of cisplatin instead of five to six cycles. In two (1.7%) patients, teleradiotherapy dose was limited to 40 Gy instead of the planned 50 Gy. The reason for limiting the dose of chemo- or radiotherapy was mostly acute haematological toxicity (ten patients) and then gastrointestinal disorders (eight patients), disease progression (two patients), exacerbation of accompanying diseases (four patients), and further chemotherapy refusal (two patients).

The aforementioned results present the current authors' observations regarding early chemoradiation toxicity in cervical cancer patients and are entirely consistent with literature reports in terms of type as well as incidence rate. The majority of authors emphasize that haematological, gastrointestinal, and urinary tract disorders constitute an overwhelming part of acute complications and most of them are of grade 1 or 2. In terms of incidence and causes, limitations introduced to the course of planned treatment are also in line with literature data. The authors underscore that in 25% up to 33% of patients, it is not possible to complete full chemoradiotherapy [3, 7, 10, 11, 13, 14, 20-25, 35-39].

In the material analysed by Reig *et al.* [23], almost all 56 patients developed acute haematological toxicity including anaemia of grade 1-2 in 94.5% of cases and of grade 3-4 in 5.2%; leucopenia of grade 1-2 in 49.9% of cases, and of grade 3 in 30.3%. Acute gastrointestinal toxicity of grade 1-2 was observed in 89.2% of the group and of grade 3 in 10.7%. Acute urinary tract infections of grade 1-2 were reported in 49.1% and of grade 3 in 25.0% of the patients. Acute vaginal mucositis of grade 1-2 occurred in 64.2% of the women and of grade 3 in 16.0% of them. Six cycles of chemotherapy was given to 67.8% of patients, five cycles to 19.6%, and four cycles to 13.5%; the main reason for reducing the number of cycles was leucopenia.

In the 74-patient study group presented by Tana *et al.*, (25) the most common adverse side-effects were: diarrhea in 80.6% of patients, malaise in 66.7%, and nausea in 62.5%. Anaemia of grade 1-2 occurred in 41.7% of the patients and of grade 3-4 in 4.2%. One patient developed grade 3 thrombocytopenia and another one neutropenia of grade 4. In the group, 97.3% of patients completed external beam radiotherapy and 70.2% of them completed the planned number of chemotherapy cycles.

In the study of 92 patients by Parker *et al.* [3], 98.9% of the group completed the planned radiotherapy (external + brachytherapy). Planned five cycles of chemotherapy were given to 62 patients (67.4%), four cycles to 21 (22.8%), three cycles to six (6.5%), two cycles to two (2.2%), and one cycle to one (1.1%).

In the Lukka *et al.,* meta-analysis of randomized trials of cisplatin-based chemoradiotherapy [8], the reported rates of acute grade 3 or 4 toxicity ranged from four to 47% (mean: 23%) for haematological toxicity, zero to 15% (mean: 9%) for gastrointestinal toxicity, and one to eight percent (mean: 2%) for genitourinary toxicity.

Table 5 – *Late toxicity (grade 3 and 4) of CCRT in LACC patients*

| Authors, reference entry number | Year of publication | Late toxicity of grade 3 or 4 [%] |
|---|---|---|
| Eifel et al. (53) | 2004 | 12.6% |
| Toita et al. (50) | 2005 | 2.5% |
| King et al. (47) | 2006 | 12.7% |
| Chen et al. (54) | 2006 | 14.3% |
| Novetsky et al. (49) | 2007 | 6.0% |
| Rose et al. (52) | 2007 | 2.8% |
| Atahan et al. (51) | 2007 | 8.0% |
| Tan and Zahra (22) | 2008 | 18.3% |
| Parker et al. (3) | 2009 | 4.0% |
| Spensley et al. (20) | 2009 | 9.3% |
| Vale et al. (21) | 2010 | 10.0% |

*Late toxicity*

Late treatment complications were observed in 18 (15%) cases, 16 (13.3%) of which were mild complications (grade 1 or 2) including persistent diarrhea, rectal bleeding, chronic cystitis, and vagina narrowing. The complications were managed with conservative treatment and, in the majority of patients, the symptoms subsided within few months or were considerably reduced (e.g. vagina narrowing).

Severe (grade 3 or 4) late complications were observed in two patients (1.6%) of the investigated group. One patient developed narrowing of large intestine, which required operational intervention, and another one recto-vaginal fistula.

Observed in the investigated group, 15% late toxicity rate, including 1.6% rate of sever toxicities (grade 3 or 4), is similar to that reported in the literature wherein late toxicity rate varies between ten and even 25% with severe complications rate of one percent to even 18% (3, 5, 10, 14, 20-25, 30, 38-41). Table 5 presents the above data.

A meta-analysis of 19 trials by Kirwan *et al.* reported 11 toxic deaths, eight acute (sepsis), and three late toxicities (small bowel obstruction, ureteral fibrosis, and pulmonary embolus) [10]. A recent UK series presented by Tan and Zahra reported late grade 3 and 4 toxicity rate of 18.3%, with three toxic deaths. Thirteen of 71 patients (18.3%) had one complication that was classified as grade 3 or 4: 8.5% had urinary complications (frequency, haematuria, and cystostomy), 70% bowel complications (diarrhea, rectal bleeding, ileus, and colostomy), and 8.5% complications affecting other organs (cervix ulcer, sensory or motor neuropathy, vascular necrosis of hips). Five patients had grade 3 or 4 complications affecting more than one organ (22). In the analysis of 75 patients by Spensley *et al.*, late toxicity was reported in seven (9.3%), including three patients with bowel toxicity requiring surgery (rectal fistula, sigmoid stricture, and small bowel obstruction), three patients with bladder toxicity, and one patient with vaginal stenosis [20]. In the Vale *et al.* study to present the results of Royal College of Radiologists audit (2001-2002), grade 3/4 late toxicity was observed in ten percent of 471 patients treated with CCRT + RT; the complications occurred in vagina (5%), rectum (3%), colon (1.5%), small bowel (1%), and bladder (2%) [21]. Of the 92 patients presented by Parker *et al.*, four (4%) had late toxicities of grade 3 or 4 (recto-vaginal fistula requiring colostomy, delayed osteonecrosis of the hips requiring total hip replacement, vaginal bleeding requiring hysterectomy, and vesico-vaginal fistula requiring the formation of an artificial bladder) [3].

*CCRT vs. RT alone (acute and late toxicity)*

In the literature, the discussion is held whether CCRT does increase severity of acute and late toxicity [3, 5, 7-10, 13, 14, 20-25, 27-30].

In the meta-analysis presented by Green *et al.* (2001) and Lukka et al. (2002), late toxicity of CCRT was examined; no differences were found in the rates of bowel or bladder toxicities between patients treated with RT alone and those treated with CCRT [7, 8].

In 2003, Kirwan *et al.* showed that grade 1 and 2 acute haematological toxicities were higher in CCRT than in RT alone group and significant differences were seen in grade 3 and 4 acute haematological and gastrointestinal toxicities; however, the authors concluded that "in view of the consistency and extent of the survival benefit for CCRT, the additional acute toxicity appears to be acceptable " [10].

Published in 2008, meta-analysis from Meta-Analysis Group, Medical Research Council Clinical Trials Unit (Vale *et al.*), showed that acute haematological and G1 toxicity was increased with CCRT, but data was too sparse for an analysis of late toxicity [24].

The study presented by Tan and Zahra showed that the addition of chemotherapy to radiotherapy for cervical cancer increased risk of serious late toxicity [22], while Parker *et al.* reported in their study that the presented regimen (CCRT + high-dose rate brachytherapy) is effective with acceptable long-term side effects [3].

Spensley *et al.* established in their study that late toxicity rate increased to 9.3% compared with 3.4% reported by Denton *et al.* in 2000 [48] for national audit patients treated in 1993; the increase, however, was not statistically significant. Acute toxicity is increased in CCRT "but with careful monitoring and evaluation of the patient during treatment is manageable" [20].

In 2010, Vale *et al.* presented results of a Royal College of Radiologists audit. In the group of 355 patients treated with RT only, late complications of grade 1 and 2 were found in 43% of women, and of grade 3 and 4 in eight percent; whereas in the CCRT group, the rate was 47% and 10%, respectively, "without an apparent rise in late complications" [21].

The acute and long-term toxic effect of CCRT is one of major challenges in LACC patients. Attempts to limit the toxic effect are currently focused on three major fields: investigation of new cytotoxic chemotherapy agents (gemcitabine and topotecan) and biologically targeted agents (3-AP, tirazapamina, and avastin); more sophisticated radiology for radiotherapy planning (CT, MRI, positron emission tomography - PET), as well as advances in radiotherapy technique (intensity-modulated radiation therapy – IMRT, image-guided brachytherapy), and improved supportive care (antiemetic, growth factors) [5, 14, 20-22, 30].

## Conclusions

In patients with LACC treated with CCRT, the most frequent acute toxic effects include: haematological disorders (anaemia, neutropenia, thrombocytopenia), gastrointestinal disorders (nausea and vomiting, and diarrhea), vulvo-vaginal disorders, and urinary tract infection; the most frequent late toxic effects include: gastrointestinal disorders (diarrhea, rectal bleeding, bowel complications requiring surgery), vaginal disorders (fibrosis, stenosis, recto–vaginal fistula), urological disorders (frequency, haematuria, vesico-vaginal fistula, cystectomy), and cervix ulcer. Rate and severity of CCRT toxicity may be reduced by investigation of new agents, advances in radiation therapy, and optimal supportive care.

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