Clinics in Oncology

Research Article
Published: 22 Mar, 2017

Clinical Outcomes of Adjuvant Therapies in Early Stage Invasive Cervical Cancer: More Research is Needed

*Luz Angela Torres-de la Roche[1] and Rudy Leon De Wilde[2]**

[1]Department of Gynecology, University Medical School, Germany

[2]Department of Obstetrics and Gynecological Oncology, Carl von Ossietzky University Medical School, Germany

Abstract

Introduction: Uterine cervical cancer is one of the most common malignancies worldwide and the second most common gynecological cancer, specifically within the age group of 55–59 years. With the advancement in effective screening methods and treatment, patients with early stage disease have better prognosis now than before, but the impact of those therapies is not well known. The aim of this paper is to have a background about neoadjuvant therapies for early stage invasive cervical cancer, in order to guide our future research activities.

Methods: Searches were conducted in PubMed, Medline, Orbisplus, Google Scholar and The Cochrane Library to identify relevant literature in English and German.

Results: There is limited evidence about side effects of the combined radio-chemotherapy for uterine cervical cancer stages IIA und IIB. It was found no significant difference in survival at 5 years between women who received adjuvant therapy after surgery and those who received no further treatment (RR = 0.8; 95% IC 0.3-2.4), but the risk of disease progression was low for those who received radiation.

Conclusion: More research is needed to add to the international knowledge about the effects of the therapies on the quality of health of the women with early invasive uterine cervical cancer. Furthermore, on the quality of care offered in different Cancer Centers.

Keywords: Cervix uteri/radiation effects; Radiotherapy/radiotherapy adjuvant; Combined modality therapy; Antineoplastic combined chemotherapy protocols

OPEN ACCESS

Correspondence:
Rudy Leon De Wilde, Department of Obstetrics and Gynecological Oncology, Carl von Ossietzky University Medical School, Germany, Tel: 49 0 441 229 1524;
E-mail: rudy-leon.dewilde@pius-hospital.de

Received Date: *25 Jan 2017*
Accepted Date: *06 Mar 2017*
Published Date: *22 Mar 2017*

Citation:
Torres-de la Roche LA, De Wilde RL. Clinical Outcomes of Adjuvant Therapies in Early Stage Invasive Cervical Cancer: More Research is Needed. Clin Oncol. 2017; 2: 1237.

Introduction

Uterine Cervical Cancer(UCC) is one of the most common malignancy worldwide, with 58.348 new affected women in Europe (Incidence rate 13.4/100.000) and a mortality rate of 4,9/100000 women (IARC, 2012). It is the tenth most common cancer in German women (2.8% of all cases), specifically within the age group of 55–59 years, and the second most common gynecological cancer, with 4.995 new cases in 2012 (Incidence rate 9,8/100.000), and a mortality rate of 2,4/100.000 , that is 1,566 deaths [1].

In Germany, the screening UCC program has been performed since 1971 and currently is made by a decentralized organization with exclusive involvement of gynecologist and pathologist, and it is recognized because of its high quality and gratuity [2]. However, only 79% of eligible population is reached, especially younger women, married women, and those with higher education [3]. Here, a low self-conscientious of the women, derived of a lack of knowledge about the risks and benefits of the pap smear, appears as a decisive contributing factor for new cases of advanced UCC. Consequently, losing the opportunity for conservative and fertility sparing interventions and diminishing the survival rate. As a matter of fact, in 2012, 62% of cases were diagnosed in stage T1, 25% in stage T2, 8% in stage T3, and 6% in stage T4 (AWMF, 2014). Other well known risk factors for UCC are early sexual activity, multiple sexual partners, cigarette smoking and persistent infection of the cervix by the Human Papilloma Virus [HPV]. It is expected that the development and introduction of vaccination against HPV in 2007 by the German Standing Vaccination Committee, helps in the declination of incidence and mortality rates of HPV related UCC (AWMF, 2014). With the advancement in screening and treatment methods, patients with UCC have better prognosis now than before, although the survival rate is also influenced by histologic type (Port, 2011), giving adenocarcinoma the lowest rates in five years (Table1), and by tumoral intrinsic factors like: localization (endo/exocervix), staging at diagnosis (TNM status), resection borders (R-classification),

Table 1: Relative 5 survival rates of German women with uterine cervical cancer. According to FIGO classification:

	TNM stage of disease				
	0	I	II	III	IV
Squamous cell	100	83%	62%	42%	18%
Adenocarcinoma	100	51%	44%	17%	0%
UCC 0 = TIS N0 M0; in situ. UCC I = T1 N0 M0; UCC II = T2 N0 M0; UCC III = T3 N0 M0 or T1-3 N1 M0; UCC IV = T4 N0 M0 or T4 N1 M0 or any T of any N M					
Font: Based on Port, 2011					

perineuralinfiltration (Pn-Status), infiltration of lymph vessels (L-Status), invasion of venules (V-Status), Grading, p16, Ki-67 status, deep infiltration, and lymph nodes immunohistochemistry (AWMF, 2014). According to the recommendations of the German guidelines (AWMF, 2014), the complete staging procedures in women of any age without the desire of organ preservation include: inspection and palpation of the entire abdominal cavity, with Bilateral Salpingo-Oophorectomy (BSO), total hysterectomy, infracolic omentectomy, abdominal washing, multiple biopsies of peritoneal surfaces and sampling of pelvic and para-aortic lymph nodes. Laparoscopy is the preferred method for younger women undergoing conservative treatment, meaning they wish to preserve their uterus or fertility, and at least part of one ovary is salvageable, but with all other above named surgical steps followed.

Therapies offered to these women depend on the extend of the disease and the woman´s reproductive desire. Once a woman is detected to have an abnormal Pap smear, a subsequent conization could confirm the diagnosis, and at same time could be the definitive treatment in cases of pre invasive stages of UCC. Low complication rates are reported for this procedure. For advanced UCC, currently treatment modalities, either radical surgery, radiotherapy or neoadjuvant chemotherapy, are associated with long term side effects (Grigsby, 2001; Health Quality Ontario [4-6]. Therefore, the aim of this paper is to have a background about neoadjuvant therapies for early stage invasive cervical cancer, in order to guide our future research activities**.**

Methods

In order to identify relevant literature published in English and German related to our topic, searches were conducted in PubMed, Medline, Orbis plus, Google scholar and in the Cochrane Library by using the following MeSH Terms: Cervix Uteri/pathology, Cervix Uteri/radiation effects; Uterine Cervical Neoplasms/radiotherapy, Uterine Cervical Neoplasms/surgery, Radiotherapy/Radiotherapy adjuvant, Brachytherapy, Chemoradiotherapy, Combined Modality Therapy/ Antineoplastic Combined Chemotherapy Protocols.

Results

Combined weekly radiotherapy and cisplatin without hysterectomy could be considered for patients with stage IB. For patients with stages IIA and IIB, radical surgery followed by pelvic radiation and 3-4 cycles of chemotherapy is recommended. However, the evidence indicates no significant difference in survival at 5 years between women who received adjuvant therapy after surgery and those who received no further treatment (RR=0.8; 95% IC 0.3-2.4), but the risk of disease progression was low for those who received radiation [7]. Because of potential risk of recurrence, IUCC patients should be evaluated every 3 months within the first 2 years following initial surgery, biannually for 3-5 years after surgery, and annually thereafter. Monitoring must be conducted via Pap test and clinical examination, including transvaginal and transabdominal ultrasound, which make detection of small abnormalities and extra pelvic implants possible. High risk factors for recurrence include tumor size, depth of invasion, lymph vascular space involvement and lymph node involvement. When a recurrence is suspected, it is mandatory to confirm the diagnosis through colposcopy and biopsy, and look for metastasis through pelvic MRI, cystoscopy, proctoscopy, TAC of thorax and abdomen [8]; AWMF, 2014). According to the site of recurrence, 40 -60% of cases will be loco-regional, 20 – 40% will have distant metastasis, and 10 – 20% of cases will have local and distant metastasis (AWMF, 2014). These cases will require an individualized therapy, according to the clinical findings and patient´s desire.

In regards to complications, Minimal Invasive Procedures [MIS] are recognized to have more benefits for patients (Health Quality Ontario, 2010), including decreased blood loss, reduced postsurgical pain, short hospitalization, improved cosmetic results and faster recovery, but robotics show fewer conversions to laparotomy (1% *vs.* 10%). Medial incisions are associated with increased postoperative analgesic requirements, longer hospitalization, slower recovery time and higher morbidity rates. Although, there were no differences encountered between the approaches for operation time and lymph node recovery, but significant differences when comparing different surgical approaches - laparotomy [LPM], laparoscopy [LSK] or robotics [RB]: median post-operative hospital stay (RB: 7.9 *vs.* LSK: 7.7 *vs.* LPM: 10.8 days, $p < 0.001$); overall complications (RB: 7.1 *vs.* LSK: 8 *vs.* LPM: 25%, $p = 0.049$), and transfusions (RB: 14.3 *vs.* LSK: 16 *vs.* LPM: 42.9%, $p = 0.006$). Concluding that LPM had more detrimental effects compared to MIS, specially due to wound dehiscence complications. In contrast, the LPM group showed an increased number of pelvic lymph nodes recovered, followed by RB, and then the LSK (RB: 21.1 *vs.* LSK: 18.4, *vs.* LPM: 24.4, $p = 0.024$). In addition, obese patient had an increased surgical risk and perioperative morbidity indistinctly of the procedure.

Discussion

In the last years the effort is given not only to improve the recurrence and survival rates of patients with advanced UCC, but to analyze those short and long term impacts of the recommended treatments. Long term sequela of all therapies for IUCC [9], are derived of extension of the procedure, the surgical technique or the combination of therapies. They are also related with the physical and psychosocial domains of the woman, such as anxiety, depression, dysfunction of the pelvic organs and sexual dysfunction [10]. Contrary, few studies are conducted evaluating long term effect of radio-chemotherapy for patients with UCC stage IB, IIA und IIB [11]. Some studies in this area [10-12], conclude that this knowledge allows physicians to improve the information they give during the counseling sessions, and help patients in the decision-making process related with their therapy and subsequent self-care. According to treatment modality, radical procedures and radiotherapy are more related with anorectal dysfunction, urinary symptoms, vaginal dryness, short vagina, dyspareunia and lymphedema. Evidently, all mentioned complications affect significantly the woman´s quality of life. Based on the limited evidence about side effects of the combined radio-chemotherapy for patients with UCC stage IB, IIA and IIB, we are conducting a single-Institution retrospective review of the clinical

outcomes of this therapy, which results will be published in short. The ultimate purpose is to add to the international knowledge in this field.

Conclusion

More research is needed about the effects of the therapies on the quality of health of the women with early invasive uterine cervical cancer. Therefore, we recommend the realization of studies that allow analyzing the impact of those therapies on women´s health and women´s lives. Moreover, such research could give feedback to researchers and physicians about the quality of care offered in their Cancer Centers.

References

1. AWMF. S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit ZervixkarzinomKurzversion 1.0 – September. 2014.
2. Butler-Manuel SA, Summerville K, Ford A, Blake P, Riley AJ, Sultan AH, et al. Self-assessment of morbidity following radical hysterectomy for cervical cancer. J Obstet Gynaecol. 1999; 19: 180-183.
3. Dreier M, Borutta B, Töppich J, Bitzer EM, Walter U. Früherkennung von Brust- und Gebärmutterhalskrebsein systematischer Review zu Wissen, Einstellungen und Inanspruchnahmeverhalten der Frauen in Deutschland. Gesundheitswesen. 2012; 74: 722-735.
4. Grigsby PW. Cervical cancer: combined modality therapy. Cancer J. 2001; 7: S47-S50.
5. Health Quality Ontario. Robotic-Assisted Minimally Invasive Surgery for Gynecologic and Urologic Oncology: An Evidence-Based Analysis. Ont Health Technol Assess Ser. 2010; 10: 1-118.
6. Hsu WC, Chung NN, Chen YC. Comparison of surgery or radiotherapy on complications and quality of life in patients with the stage IB and IIA uterine cervical cancer. Gynecol Oncol. 2009; 115: 41-45.
7. IARC- International Agency for Research on Cancer, Cervical cancer. Estimated incidence, mortality & prevalence. 2012.
8. Khalil J, Bellefqih N, Sahli M, Afif H, Elkacemi S, Elmajjaoui, et al. Impact of cervical cancer on quality of life: beyond the short term (Results from a single institution). Gyn Oncol Res Pract. 2015; 2: 7.
9. PORT (Projekt offene radioonkologische Therapiedatenbank). Zervix Carcinom. 2016.
10. Rogers L, Siu SSN, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. Cochrane Database Systematic Reviews. 2012.
11. Schneider V. Gynäkologische Krebs-vorsorge in Deutschland. Gegenwärtiger Stand. Pathologe. 2012.
12. Ye S, Yang J, Cao D, Lang J, Shen K. Systematic Review of Quality of Life and Sexual Function of Patients With Cervical Cancer After Treatment. Int J Gyn Cancer. 2014; 24: 1146-1157.