



New Insights in Endometrial Cancer Treatment

Androutsopoulos G*, Michail G and Decavalas G

Department of Obstetrics and Gynecology, University of Patras, Medical School, Rion, Greece

Editorial

Nowadays, endometrial cancer (EC) represents the most common malignancy of the female genital tract in developed countries [1-5]. The estimated average life time risk for EC in the United States, is approximately 2.64%. EC most commonly occurs in postmenopausal women [1-5]. The sporadic EC based on its clinical and pathological features is classified into 2 different types (type I EC and type II EC) and the classification has a crucial role for the entire management of EC patients [6,7]. It is interesting to note, that the international scientific societies (ACOG, FIGO, SGO and ESMO) recommend the systematic surgical staging as the initial treatment approach in patients with EC [3-5,8-12]. More specifically, the systematic surgical staging in patients with type I EC (endometrioid) includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and complete resection of any suspicious lesion [2-5,8-15]. On the contrary, the systematic surgical staging in patients with type II EC (poorly differentiated, papillary serous, clear cell) includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, total omentectomy, appendectomy and complete resection of any suspicious lesion [3-5,10,11,14-16]. Additionally, pelvic washings are necessary for both types of EC, although they do not affect FIGO staging [9]. The systematic surgical staging in patients with EC can be performed either with laparotomy or laparoscopy [2-5,8,10-12,17-20]. When applied in EC patients, both of them have similar results in recurrence rates and they associated with similar overall and disease-free survival rates [10,12,17,18]. Nevertheless, minimally invasive techniques have significant advantages especially in overweight and elderly patients (smaller incisions, improved visualization, shorter hospital stay, less postoperative pain, quicker recovery and low risk for postoperative complications) [3-5,8,10-12,17-21]. Laparotomy is the most preferable approach for systematic surgical staging in patients with EC [3-5,10,11,17,18]. In sharp contrast, minimally invasive techniques (laparoscopy and robotic-assisted surgery) are significantly more difficult and time consuming and require special surgical skills [2-5,8,10-12,17-20]. This is the reason why, minimally invasive techniques are less popular and we use them only in EC patients with early stage disease [2-5,8,10-12,17-20]. It is also worth noting, that pelvic and para-aortic lymphadenectomy has an essential role for systematic surgical staging in patients with EC [3-5,11,14,15]. It is the only way to diagnose EC patients at stage IIIc [3-5,8,9,11-13,22,23]. Furthermore, pelvic and para-aortic lymphadenectomy improves survival in patients with advanced stage type I EC and in all patients with type II EC [2-5,11,24-28]. In contrast, pelvic and para-aortic lymphadenectomy do not improve survival in patients with early stage type I EC [2-5,11,12,29,30]. Nevertheless, the extent of pelvic and para-aortic lymphadenectomy (>14 lymph nodes) in patients with EC, increases significantly the risk for postoperative complications [3-5,11,29,31,32]. As a consequence, in elderly patients and in patients with relative comorbidities (obesity, diabetes and coronary artery disease) we should carefully weigh the increased intraoperative and postoperative morbidity with any survival advantage [3-5,8,11,31,33,34]. On the other hand, according to the recommendations of the international scientific societies (ACOG, SGO and ESMO), postoperative adjuvant treatment (radiotherapy and/or chemotherapy) plays a very important role in EC patients with increased risk for recurrence or at advanced stage disease [2-5,8,10,11,13,35,36]. To begin with, the postoperative adjuvant radiotherapy in EC patients includes vaginal brachytherapy and external radiotherapy [3-5,10,11,36]. Vaginal brachytherapy is the treatment of choice in intermediate risk EC patients (stage IA grade 3 endometrioid type EC, stage IB grade 1-2 endometrioid type EC) [3-5,10,11,36-41]. The application of vaginal brachytherapy is well tolerated and it is associated with less side effects and better quality of life [10,36-40,42]. Moreover, vaginal brachytherapy minimizes the risk for local recurrences, but it does not affect overall survival [36,37,40,42]. Especially in intermediate risk EC patients, vaginal brachytherapy and external pelvic radiotherapy have an equal role for the local control of disease [3-5,10,11,36-39].

Similarly, external pelvic radiotherapy is the adjuvant treatment of choice in high risk EC patients (stage IB grade 3 endometrioid type EC, stage I non-endometrioid type EC) [3-5,10,11,38,39,42].

OPEN ACCESS

*Correspondence:

Georgios Androutsopoulos, Department of Obstetrics and Gynecology, University of Patras, Medical School, Rion 26504, Greece, Tel: +306974088092;

E-mail: androutsopoulos@upatras.gr; androutsopoulosgeorgios@hotmail.com

Received Date: 05 Jul 2016

Accepted Date: 25 Jul 2016

Published Date: 29 Jul 2016

Citation:

Androutsopoulos G, Michail G, Decavalas G. New Insights in Endometrial Cancer Treatment. Clin Oncol. 2016; 1: 1040.

Copyright © 2016 Androutsopoulos G. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The application of external pelvic radiotherapy is not well tolerated and it is associated with significant morbidity and reduction in quality of life [3-5,11,37,43]. Although external pelvic radiotherapy minimizes the risk for local recurrences, it does not affect overall survival [8,36-38,40,43,44]. In contrast, whole abdomen radiotherapy is an alternative treatment option in EC patients with advanced stage disease [45]. However, whole abdomen radiotherapy should be used only in patients with completely resected disease [45]. Furthermore, it has tolerable toxicity and may improve overall survival [3-5,11,45]. On the other hand, postoperative adjuvant chemotherapy is the adjuvant treatment of choice in EC patients with advanced stage disease [2-5,10,11,13,36,46,47]. Nevertheless, adjuvant chemotherapy is more effective than whole abdomen radiotherapy, in EC patients with advanced stage disease [3-5,11,35-48]. The most common used chemotherapeutic agents in EC patients, are: taxanes, anthracyclines and platinum compounds [46,49]. The application of postoperative adjuvant chemotherapy achieves high response rates, but it has only modest effect in progression free survival and overall survival [3-5,11,46]. Nowadays, the postoperative combination of adjuvant radiotherapy with adjuvant chemotherapy shows promising results, particularly in high risk EC patients and in EC patients at advanced stage disease [3-5,11,36,46,50]. Especially in EC patients with systematic surgical staging, the combined application of adjuvant radiotherapy and adjuvant chemotherapy reduces the risk of relapse or death and increases overall survival [3-5,10,11,36,51]. Additionally, the combined application of adjuvant radiotherapy and adjuvant chemotherapy is more effective than the isolated application of adjuvant radiotherapy [3-5,11,36,46,51].

Recent years, molecular targeted therapies are very popular in the treatment of various types of cancer [3-5,11]. Those therapies, usually target essential signaling pathways (EGFR, VEGFR and PI3K/PTEN/AKT/mTOR).⁵²⁻⁵⁴ However, they have not studied well in EC and they have only modest effect in unselected EC patients [3-5,11,46,55,57]. In this light, ErbB-targeted therapies can be used as an adjuvant treatment in well-defined subgroups of EC patients (type II EC) with EGFR and ErbB-2 over expression [3-5,11,14,15,54-68]. Moreover, their efficacy in those subgroups of EC patients, should be further evaluated with prospective clinical trials and adequate number of patients [3-5,11,14,15,54-68]. In conclusion, the systematic surgical staging plays an essential role in the treatment of EC patients and offers many diagnostic, prognostic and therapeutic benefits [2-5,8,11,14,15]. Moreover, it clearly affects the decision for the appropriate postoperative adjuvant treatment in EC patients, in order to maximize survival and minimize the morbidity of over-treatment (radiation injury) and the effects of under-treatment (recurrent disease, increased mortality) [2-5,8,11,14,15].

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013; 63: 11-30.
2. Sorosky J. Endometrial cancer. *Obstet Gynecol.* 2012; 120: 383-397.
3. Androutsopoulos G. Current treatment options in patients with endometrial cancer. *J Community Med Health Educ.* 2012; 2: e113.
4. Androutsopoulos G, Decavalas G. Management of endometrial cancer. *Int J Translation Community Dis.* 2013; 1: 1-3.
5. Androutsopoulos G, Michail G, Adonakis G, Decavalas G. Current treatment approach of endometrial cancer. *Int J Clin Ther Diagn.* 2015; S1:8-11.
6. Bokhman J. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol.* 1983; 15: 10-17.
7. Doll A, Abal M, Rigau M, Monge M, Gonzalez M, Demajo S, et al. Novel molecular profiles of endometrial cancer-new light through old windows. *J Steroid Biochem Mol Biol.* 2008; 108: 221-229.
8. ACOG. ACOG practice bulletin #65: management of endometrial cancer. *Obstet Gynecol.* 2005; 106: 413-425.
9. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009; 105: 103-104.
10. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013; 24: vi33-38.
11. Androutsopoulos G, Decavalas G. Endometrial cancer: current treatment strategies. *World J Oncol Res.* 2014; 1: 1-4.
12. Burke W, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye A, et al. Endometrial cancer: a review and current management strategies: part I. *Gynecol Oncol* 2014; 134: 385-392.
13. Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, Mariani A, Dowdy SC. Current issues in the management of endometrial cancer. *Mayo Clin Proc.* 2008; 83: 97-112.
14. Androutsopoulos G, Decavalas G. Endometrial cancer treatment: new insights into the role of erbb receptors. *J Gynecol Women's Health.* 2016; 1: 555552.
15. Androutsopoulos G, Adonakis G, Decavalas G. Present and future in endometrial cancer treatment. *Obstet Gynecol. Int J* 2015; 2: 00031.
16. Geisler J, Geisler H, Melton M, Wiemann M. What staging surgery should be performed on patients with uterine papillary serous carcinoma? *Gynecol Oncol.* 1999; 74: 465-467.
17. Galaal K, Bryant A, Fisher A, Al-Khaduri M, Kew F, Lopes A. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. *Cochrane Database Syst Rev.* 2012; 9: CD006655.
18. Walker J, Piedmonte M, Spirtos N, Eisenkop S, Schlaerth J, Mannel R, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. *J Clin Oncol.* 2012; 30: 695-700.
19. Walker J, Piedmonte M, Spirtos N, Eisenkop S, Schlaerth J, Mannel R, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol.* 2009; 27: 5331-5336.
20. Nezhat F. Minimally invasive surgery in gynecologic oncology: laparoscopy versus robotics. *Gynecol Oncol.* 2008; 111: S29-S32.
21. Fleming N, Ramirez P. Robotic surgery in gynecologic oncology. *Curr Opin Oncol.* 2012; 24: 547-553.
22. Creasman W, Morrow C, Bundy B, Homesley H, Graham J, Heller P. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer.* 1987; 60: 2035-2041.
23. McMeekin D, Lashbrook D, Gold M, Johnson G, Walker J, Mannel R. Analysis of FIGO Stage IIIc endometrial cancer patients. *Gynecol Oncol.* 2001; 81: 273-278.
24. Kilgore L, Partridge E, Alvarez R, Austin J, Shingleton H, Noojin F, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol.* 1995; 56: 29-33.
25. Cragun J, Havrilesky L, Calingaert B, Synan I, Secord A, Soper J, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. *J Clin Oncol.* 2005; 23: 3668-3675.
26. Lutman C, Havrilesky L, Cragun J, Secord A, Calingaert B, Berchuck A, et

- al. Pelvic lymph node count is an important prognostic variable for FIGO stage I and II endometrial carcinoma with high-risk histology. *Gynecol Oncol.* 2006; 102: 92-97.
27. Chan J, Cheung M, Huh W, Osann K, Husain A, Teng N, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer.* 2006; 107: 1823-1830.
 28. Mariani A, Webb M, Galli L, Podratz K. Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer. *Gynecol Oncol.* 2000; 76: 348-356.
 29. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst.* 2008; 100: 1707-1716.
 30. Kitchener H, Swart A, Qian Q, Amos C, Parmar M. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet.* 2009; 373: 125-136.
 31. Franchi M, Ghezzi F, Riva C, Miglierina M, Buttarelli M, Bolis P. Postoperative complications after pelvic lymphadenectomy for the surgical staging of endometrial cancer. *J Surg Oncol.* 2001; 78: 232-237; discussion 37-40.
 32. May K, Bryant A, Dickinson H, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer. *Cochrane Database Syst Rev.* 2010: CD007585.
 33. Lachance J, Darus C, Rice L. Surgical management and postoperative treatment of endometrial carcinoma. *Rev Obstet Gynecol.* 2008; 1: 97-105.
 34. Lowery W, Gehrig P, Ko E, Secord A, Chino J, Havrilesky L. Surgical staging for endometrial cancer in the elderly - is there a role for lymphadenectomy? *Gynecol Oncol.* 2012; 126: 12-15.
 35. Marnitz S, Kohler C. Current therapy of patients with endometrial carcinoma. A critical review. *Strahlenther Onkol.* 2012; 188: 12-20.
 36. Burke W, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye A, et al. Endometrial cancer: a review and current management strategies: part II. *Gynecol Oncol.* 2014; 134: 393-402.
 37. Kong A, Johnson N, Kitchener H, Lawrie T. Adjuvant radiotherapy for stage I endometrial cancer. *Cochrane Database Syst Rev.* 2012: CD003916.
 38. Nout R, Smit V, Putter H, Jurgenliemk-Schulz I, Jobsen J, Lutgens L, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet.* 2010; 375: 816-823.
 39. Chino J, Jones E, Berchuck A, Secord A, Havrilesky L. The influence of radiation modality and lymph node dissection on survival in early-stage endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2012; 82: 1872-1879.
 40. Creutzberg C, Nout R. The role of radiotherapy in endometrial cancer: current evidence and trends. *Curr Oncol Rep.* 2011; 13: 472-478.
 41. Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma: a prospective, randomized study--quality-of-life analysis. *Int J Gynecol Cancer.* 2012; 22: 1281-1288.
 42. Creutzberg C. GOG-99: ending the controversy regarding pelvic radiotherapy for endometrial carcinoma? *Gynecol Oncol.* 2004; 92: 740-743.
 43. Creutzberg C, van Putten W, Koper P, Lybeert M, Jobsen J, Warlam-Rodenhuis C, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-I endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. *Post Operative Radiation Therapy in Endometrial Carcinoma.* *Lancet.* 2000; 355: 1404-1411.
 44. Keys H, Roberts J, Brunetto V, Zaino R, Spirtos N, Bloss J, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004; 92: 744-751.
 45. Sutton G, Axelrod J, Bundy B, Roy T, Homesley H, Malfetano J, et al. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV endometrial cancer: a gynecologic oncology group study. *Gynecol Oncol.* 2005; 97: 755-763.
 46. Hogberg T. What is the role of chemotherapy in endometrial cancer? *Curr Oncol Rep.* 2011; 13: 433-441.
 47. Wright J, Barrera Medel N, Sehouli J, Fujiwara K, Herzog T. Contemporary management of endometrial cancer. *Lancet.* 2012; 379: 1352-1360.
 48. Randall M, Filiaci V, Muss H, Spirtos N, Mannel R, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2006; 24: 36-44.
 49. Fleming G, Brunetto V, Cella D, Look K, Reid G, Munkarah A, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2004; 22: 2159-2166.
 50. Schwandt A, Chen W, Martra F, Zola P, Debernardo R, Kunos C. Chemotherapy plus radiation in advanced-stage endometrial cancer. *Int J Gynecol Cancer.* 2011; 21: 1622-1627.
 51. Hogberg T, Signorelli M, de Oliveira C, Fossati R, Lissoni A, Sorbe B, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. *Eur J Cancer.* 2010; 46: 2422-2431.
 52. Dedes K, Wetterskog D, Ashworth A, Kaye S, Reis-Filho J. Emerging therapeutic targets in endometrial cancer. *Nat Rev Clin Oncol.* 2011; 8: 261-271.
 53. Tsoref D, Oza AM. Recent advances in systemic therapy for advanced endometrial cancer. *Curr Opin Oncol.* 2011; 23: 494-500.
 54. Kieser K, Oza A. What's new in systemic therapy for endometrial cancer. *Curr Opin Oncol.* 2005; 17: 500-504.
 55. Adonakis G, Androutsopoulos G. The role of ErbB receptors in endometrial cancer. In: Saldivar J, editor. *Cancer of the uterine endometrium - advances and controversies: InTech,* 2012; 23-38.
 56. Androutsopoulos G, Adonakis G, Decavalas G. ErbB targeted therapy in endometrial cancer. In: Farghaly S, editor. *Endometrial cancer: current epidemiology, detection and management: Nova Science Publishers,* 2014; 353-370.
 57. Androutsopoulos G, Adonakis G, Liava A, Ravazoula P, Decavalas G. Expression and potential role of ErbB receptors in type II endometrial cancer. *Eur J Obstet Gynecol Reprod Biol.* 2013; 168: 204-208.
 58. Konecny G, Santos L, Winterhoff B, Hatmal M, Keeney GL, Mariani A, et al. HER2 gene amplification and EGFR expression in a large cohort of surgically staged patients with nonendometrioid (type II) endometrial cancer. *Br J Cancer.* 2009; 100: 89-95.
 59. Santin A, Bellone S, Roman J, McKenney J, Pecorelli S. Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. *Int J Gynaecol Obstet.* 2008; 102: 128-131.
 60. Oza A, Eisenhauer E, Elit L, Cutz J, Sakurada A, Tsao M, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol.* 2008; 26: 4319-4325.
 61. Fleming G, Sill M, Darcy K, McMeekin D, Thigpen J, Adler L, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010; 116: 15-20.
 62. Roque D, Santin A. Updates in therapy for uterine serous carcinoma. *Curr*

- Opin Obstet Gynecol. 2013; 25: 29-37.
63. Adonakis G, Androutsopoulos G, Koumoundourou D, Liava A, Ravazoula P, Kourounis G. Expression of the epidermal growth factor system in endometrial cancer. *Eur J Gynaecol. Oncol* 2008; 29: 450-454.
64. Androutsopoulos G, Adonakis G, Gkermepesi M, Gkogkos P, Ravazoula P, Kourounis G. Expression of the epidermal growth factor system in endometrial cancer after adjuvant tamoxifen treatment for breast cancer. *Eur J Gynaecol Oncol* 2006; 27: 490-494.
65. Androutsopoulos G, Michail G, Adonakis G, Decavalas G. Molecular biology, expression and clinical significance of ErbB receptors in endometrial cancer. *Hel J Obst Gynecol* 2014; 13: 77-83.
66. Androutsopoulos G, Michail G, Adonakis G, Decavalas G. ErbB receptors and ErbB targeted therapies in endometrial cancer. *J Cancer Ther* 2014; 5: 483-492.
67. Androutsopoulos G, Michail G, Adonakis G, Decavalas G. Molecular mechanisms, expression and clinical role of ErbB receptors in endometrial cancer *Int J Clin. Ther Diagn* 2015; S1: 28-32.
68. Androutsopoulos G, Michail G, Adonakis G, Decavalas G. ErbB targeted therapy in endometrial cancer. *Int J Clin Ther Diagn* 2015; S1: 5-7.