

RECOMMENDATIONS

1. Intensity modulated radiotherapy (IMRT) for cervical carcinoma is a safe treatment with low acute toxicity. Longer follow-up is needed to assess chronic toxicity and disease control.
2. This potential new role for IMRT merits further evaluation with larger patient numbers. Whether or not these new technologies will provide benefit to the patients in terms of survival has to be further investigated in larger prospective clinical trials.
3. In centers with no or limited access to MRI, CT-based delineation of HRCTV may be applied as a tool of contouring for 3D image guided adaptive BT, especially when it is accompanied by reproducible 3D clinical drawing based on 3D precise clinical examination in addition to FIGO stage.
4. Future studies are needed to assess the reported DVH parameters for these CT based target structures in clinical practice.

REFERENCES

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin.* 2003;53:5-26.
2. Jemal A, Center MM, De Santis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev.* 2010;19:1893-1907.
3. Mathew A, George PS. Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix- worldwide. *Asian Pac J Cance Prev.* 2009; 10: 645-650.
4. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world . *J Clin Oncol.* 2006;24: 2137-50.
5. Ferenczy A, Thomas C, Wright T. Anatomy and histology of the cervix. In Kurman R. Blaustein's pathology of the female genital tract. New York: Springer-Verlag. 1994. , pp. 185-201.
6. Bosch FX, de Sanjosé S. Human papillomavirus and cervical cancer burden and assessment of causality. *J Natl Cancer Inst Monogr.* 2003;31: 3-13.
7. Sancho-Garnier H, Khazraji YC, Cherif MH, Mahnane A, Hsairi M, El Shalakamy A, et al. Overview of cervical cancer screening practices in the extended Middle East and North Africa countries. *Vaccine.* 2013; 30: 51-7.
8. Hill EC. Clear cell carcinoma of the cervix and vagina in young women. A report of six cases with association of maternal stilbestrol therapy and adenosis of the vagina. *Am J Obstet Gynecol.* 1973;116:470.
9. Melnick S, Cole P, Anderson D. Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix: an update. *N Engl J Med.* 1987; 316:514.
10. Herrero R, Brinton LA, Reeves WC, Brenes MM, Tenorio F, de Britton RC, et al. Sexual behavior, venereal diseases, hygiene practices, and invasive cervical cancer in a high-risk population. *Cancer.* 1990;65:380-6
11. Palefski JM, Holly EA. Molecular virology and epidemiology of human papillomavirus and cervical cancer. *Cancer Epidemiol Biomarkers Prev.* 1995;4:415-28.
12. National Institutes of Health Consensus Development Conference statement on cervical cancer. April 1-3, 1996. *Gynecol Oncol.* 1997;66:351-61.
13. Lee SJ1, Yeo SG, Park DC. High-risk human papillomavirus infection in low risk women: incidence, patient characteristics, and clinical meaning for cervical cancer. *Int J Med Sci.* 2012;9:103-7.

References

14. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999; 189:9-12.
15. Muñoz N. Human papillomavirus and cancer: the epidemiological evidence. *J Clin Virol.* 2000;19:1-5.
16. Thomsen LT, Frederiksen K, Munk C, Junge J, Iftner T, Kjaer SK. Long-term risk of cervical intraepithelial neoplasia grade 3 or worse according to high-risk human papillomavirus genotype and semi-quantitative viral load among 33,288 women with normal cervical cytology. *Int J Cancer.* 2014;1002:29-37.
17. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet.* 2007;370: 890-907.
18. Zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. *J Natl Cancer Inst.* 2000; 92: 690-8.
19. Feingold AR, Vermund SH, Burk RD, Kelley KF, Schragger LK, Schreiber K, et al. Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr.* 1990;3:896-903.
20. Olsson SE, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. *Hum Vaccin.* 2009;5:696-704.
21. P Sasieni, J Adams and J Cuzick. Benefits of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer.* 2003; 89:88-93.
22. Albrow R, Kitchener H, Gupta N, Desai M. Cervical screening in England: the past, present, and future. *Cancer Cytopathol.* 2012;120:87-96.
23. Smith, RA, Cokkinides V, Brawley O. Cancer screening in the United States, A review of current American Cancer Society guidelines and cancer screening issues. *Cancer J Clin.* 2008;58:161-79.
24. Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol.* 1998; 92: 727-35.
25. Holowaty P, Miller AB, Rohan T. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst.* 1999;91:252-8.
26. Green GH, Donovan JW. The natural history of cervical carcinoma in situ. *Obstet Gynaecol Br Common J.* 1970; 77:1-9.
27. McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma in situ of the cervix. *Obstet Gynecol J.* 1984;64:451-8.

References

28. Schneider V. Should the Bethesda System terminology be used in diagnostic surgical pathology? *Counterpoint. Int J Gynecol Pathol.* 2003;22:7-13.
29. Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med J.* 2003; 127: 946-9.
30. Solomon D. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses: developed and approved at the National Cancer Institute Workshop in Bethesda, Maryland, December 12-13, 1988. *Hum Pathol.* 1990 ;2:704-8.
31. Fife KH, Cramer HM, Schroeder JM, Brown DR. Detection of multiple human papillomavirus types in the lower genital tract correlates with cervical dysplasia. *J Med Virol.* 2001;64:550-9.
32. Reich O, Pickel H, Tamussino K, Winter R. Microinvasive carcinoma of the cervix: site of first focus of invasion. *Obstet Gynecol.* 2001; 97: 890-2.
33. Creasman WT, Zaino RJ, Major FJ, DiSaia PJ, Hatch KD, Homesley HD. Early invasive carcinoma of the cervix (3 to 5 mm invasion): risk factors and prognosis. A Gynecologic Oncology Group study. *Am J Obstet Gynecol.* 1998;178:62-5.
34. Robert ME, Fu YS. Squamous cell carcinoma of the uterine cervix: a review with emphasis on prognostic factors and unusual variants. *Semin Diagn Pathol.* 1990;7:173.
35. Frega A, Lukic A, Nobili F, Palazzo A, Iacovelli R, French D, et al. Verrucous carcinoma of the cervix: detection of carcinogenetic human papillomavirus types and their role during follow-up. *Anticancer Res.* 2007;27:4491-4.
36. Trivijitsilp P, Mosher R, Sheets EE, Sun D, Crum CP. Papillary immature metaplasia (immature condyloma) of the cervix: a clinicopathologic analysis and comparison with papillary squamous carcinoma. *Hum Pathol.* 1998;29:641-8.
37. Young RH, Clement PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. *Histopathology.* 2002;41:185-207.
38. Ferry JA, Scully RE. Adenoid cystic carcinoma and adenoid basal cell carcinoma of the uterine cervix: a study of 28 cases. *Am J Surg Pathol.* 1988;12:134-44..
39. Viswanathan AN, Deavers MT, Jhingran A, Ramirez PT, Levenback C, Eifel PJ. Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. *Gynecol Oncol.* 2004;93:27-33.
40. Inoue T. Prognostic significance of the depth of invasion relating to nodal metastases, parametrial extension, and cell types. A study of 628 cases with Stage IB, IIA, and IIB cervical carcinoma. *Cancer.* 1984;54:30-35.
41. Berman ML, Keys H, Creasman W. Survival and patterns of recurrence in cervical cancer metastatic to periaortic lymph nodes (Gynecologic Oncology Group study). *Gynecol Oncol.* 1984;19:8-16.

References

42. Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin.* 2002;52:342-62.
43. Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systemic review. *Ann Intern Med.* 2000;132:810-19.
44. Benedet JL, Anderson GH, Boyes DA. Colposcopic accuracy in the diagnosis of microinvasive and occult invasive carcinoma of the cervix. *Obstet Gynecol.* 1985;65:55-7.
45. Temkin SM, Hellmann M, Lee YC, Abulafia O. Dysplastic endocervical curettings: a predictor of cervical squamous cell carcinoma. *Am J Obstet Gynecol.* 2007;196:469.e1-4.
46. Luesley DM, Cullimore J, Redman CW, Lawton FG, Emens JM, Rollason TP, et al. Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears. *Br Med J.* 1990;300:1690-3.
47. Wong TZ, Jones EL, Coleman RE. Positron emission tomography with 2-deoxy-2-[(18)F]fluoro-d-glucose for evaluating local and distant disease in patients with cervical cancer. *Mol Imaging Biol J.* 2004; 6: 55-62.
48. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin.* 2007;57:43–66.
49. Sironi S, Buda A, Picchio M, Perego P, Moreni R, Pellegrino A, et al. Lymph node metastasis in patients with clinical early-stage cervical cancer: detection with integrated FDG PET/CT. *Radiology.* 2005;238:272–9.
50. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. FIGO committee on gynecologic oncology. *Int J Gynaecol Obstet.* 2009;105:103-4.
51. Eifel PJ, Morris M, Wharton JT, Oswald MJ. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1994; 29:9-16.
52. Kristensen GB, Abeler VM, Risberg B, Trop C, Bryne M. Tumor size, depth of invasion, and grading of the invasive tumor are the main prognostic factors in early squamous cell cervical carcinoma. *Gynecol Oncol.* 1999;74:245-51.
53. Delaloye JF, Pampallona S, Coucke PA, De Grandi P. Younger age as a bad prognostic factor in patients with carcinoma of the cervix.. *Eur J Obstet Gynecol Reprod Biol.* 1996;64:201-5.

References

54. Dattoli MJ, Gretz HF III, Beller U, Lerch IA, Demopoulos RI, Beckman EM, et al. Analysis of multiple prognostic factors in patients with stage IB cervical cancer: age as a major determinant. *Int J Radiat Oncol Biol Phys.* 1989;17:41-7.
55. Häckel M, Schlenger K, Mitze M, Schäffer U, Vaupel P. Hypoxia and radiation response in human tumors. *Semin Radiat Oncol.* 1996;6:3-9.
56. Haensgen G, Krause U, Becker A, Stadler P, Lautenschlaeger C, Wohlrab W, et al. Tumor hypoxia, p53, and prognosis in cervical cancers. *Int J Radiat Oncol Biol Phys.* 2001;50:865-72.
57. Delgado G, Bundy BN, Fowler WC, Stehman FB, Sevin B, Creasman WT, et al. A prospective surgical pathological study of stage I squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1989;35:314-20.
58. Perez CA, Grigsby PW, Nene SM, Camel HM, Galakatos A, Kao MS, et al. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. *Cancer.* 1992;69:2796-806.
59. Leveque J, Laurent JF, Burtin F, Foucher F, Goyat F, Grall JY, et al. Prognostic factors of the uterine cervix adenocarcinoma. *Eur J Obstet Gynecol Reprod Biol.* 1998;80:209-14.
60. Manusirivithaya S, Isariyodom P, Charoeniam V, Pantusart A. Risk for radical hysterectomy failure. *J Med Assoc Thai.* 2001;84:791-7.
61. Inoue T, Morita K. The prognostic significance of number of positive nodes in cervical carcinoma stages IB, IIA, and IIB. *Cancer.* 1990;65:1923-7.
62. Alfsen GC, Kristensen GB, Skovlund E, Pettersen EO, Abeler VM. Histologic subtype has minor importance for overall survival in patients with adenocarcinoma of the uterine cervix: a population-based study of prognostic factors in 505 patients with nonsquamous cell carcinoma of the cervix. *Cancer.* 2001;92:2471-83.
63. Loncaster JA, Cooper RA, Logue JP, Davidson SE, Hunter RD, West CM. Vascular endothelial growth factor (VEGF) expression is a prognostic factor for radiotherapy outcome in advanced carcinoma of the cervix *Br J Cancer.* 2000;83:620-25.
64. Ohno T, Nakano T, Niibe Y, Tsujii H, Oka K. Bax protein expression correlates with radiation-induced apoptosis in radiation therapy for cervical carcinoma. *Cancer.* 1998;83:103-10.
65. Harima Y, Nagata K, Harima K, Oka A, Ostapenko V, Shikata N, et al. Bax and Bcl-2 protein expression following radiation therapy versus radiation plus thermoradiotherapy in stage IIB cervical carcinoma. *Cancer.* 2000;88:132-8.
66. Tsai CC, Liu YS, Huang SC, Huang SC, Chang HW, Tseng CW, et al. Value of preoperative serum CA 125 in early-stage adenocarcinoma of the uterine cervix without pelvic lymph node metastasis. *Gynecol Oncol.* 2006;100:591-5.

References

67. Tsai CC, Lin H, Huang EY, , Huang SC, Hsieh CH, Chang SY, et al. The role of preoperative serum carcinoembryonic antigen level in early-stage adenocarcinoma of the cervix. *Gynecol Oncol*. 2004;94:363-7.
68. Hou J, Goldberg GL, Qualls CR, Kuo DY, Forman A, Smith HO. Risk factors for poor prognosis in microinvasive adenocarcinoma of the uterine cervix (IA1 and IA2): a pooled analysis. *Gynecol Oncol*, 2011;121:135-42.
69. Smith HO, Qualls CR, Romero AA, Webb JC, Dorin MH, Padilla LA, et al. Is there a difference in survival for IA1 and IA2 adenocarcinoma of the uterine cervix? *Gynecol Oncol*. 2002; 85:229-41.
70. Macdonald OK1, Chen J, Dodson M, Lee CM, Gaffney DK. Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. *Am J Clin Oncol*. 2009; 32:411-6.
71. Schorge JO, Lee KR, Lee SJ, Flynn CE, Goodman A, Sheets EE. Early cervical adenocarcinoma: selection criteria for radical surgery. *Obstet Gynecol*. 1999; 94:386-90.
72. Baalbergen A, Veenstra Y, Stalpers LL, Ansink AC. Primary surgery versus primary radiation therapy with or without chemotherapy for early adenocarcinoma of the uterine cervix. *Cochrane Database Syst Rev*. 2010; 1: CD006248.
73. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet*. 1997; 350:535-40.
74. Keys HM, Bundy BN, Stehman FB, Okagaki T, Gallup DG, Burnett AF, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol*. 2003; 89:343-53.
75. Huang YT, Wang CC, Tsai CS, Lai CH, Chang TC, Chou HH , et al. Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011; 80:429-36.
76. Lea JS, Sheets EE, Duska LR, Miller DS, Schorge JO. Early-stage cervical adenocarcinoma treated by surgical intent: the role of para-aortic lymph node dissection. *Gynecol Oncol*. 2002; 84:285-8.
77. Leblanc E, Narducci F, Frumovitz M, Lesoin A, Castelain B, Baranzelli MC, et al. Therapeutic value of pretherapeutic extraperitoneal laparoscopic staging of locally advanced cervical carcinoma. *Gynecol Oncol*. 2007; 105:304-11.
78. Committee on Practice Bulletins-Gynecology ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas, number 35, May 2002. *Obstet Gynecol*. 2002; 99:855-67.

References

79. Marnitz S, Köhler C, Roth C, Füller J, Hinkelbein W, Schneider A. Is there a benefit of pretreatment laparoscopic transperitoneal surgical staging in patients with advanced cervical cancer? *Gynecol Oncol.* 2005;99:536-44.
80. Cosin JA, Fowler JM, Chen MD, Paley PJ, Carson LF, Twigg LB. Pretreatment surgical staging of patients with cervical carcinoma: the case for lymph node debulking. *Cancer.* 1998; 82:2241-8.
81. Houvenaeghel G, Lelievre L, Rigouard AL, Buttarelli M, Jacquemier J, Viens P, Gonzague-Casabianca L. Residual pelvic lymph node involvement after concomitant chemoradiation for locally advanced cervical cancer. *Gynecol Oncol.* 2006; 102:74-9.
82. Lai CH, Huang KG, Hong JH, Lee CL, Chou HH, Chang TC, et al. Randomized trial of surgical staging (extraperitoneal or laparoscopic) versus clinical staging in locally advanced cervical cancer. *Gynecol Oncol.* 2003; 89:160-7.
83. Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. *Cancer.* 2008; 112:1954-63.
84. Haie C, Pejovic MH, Gerbaulet A, Horiot JC, Pourquier H, Delouche J, et al. Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. *Radiother Oncol.* 1988; 11:101-12.
85. Rotman M, Pajak TF, Choi K, Clery M, Marcial V, Grigsby PW, et al. Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. *JAMA.* 1995;274:387-93.
86. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med.* 1999; 340:1137-43.
87. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol.* 2004; 22:872-89.
88. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol.* 1999; 17:1339-48.
89. Rose PG¹, Ali S, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation

References

- for locally advanced cervical cancer: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2007; 25:2804-10.
90. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev.* 2010;1: CD008285.
91. Dueñas-González A, Zarbá JJ, Patel F, Alcedo JC, Beslija S, Casanova L, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol.* 2011; 29:1678-85.
92. Grigsby PW, Heydon K, Mutch DG, Kim RY, Eifel P. Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys.* 2001;51:982-7.
93. Beriwal S, Gan GN, Heron DE, Selvaraj RN, Kim H, Lalonde R, et al. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2007; 68:166-71.
94. Esthappan J, Chaudhari S, Santanam L, Mutic S, Olsen J, Macdonald DM, et al. Prospective clinical trial of positron emission tomography/computed tomography image-guided intensity-modulated radiation therapy for cervical carcinoma with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys.* 2008;72:1134-9.
95. Iwasaka T, Fukuda K, Hara K, Yokoyama M, Nakao Y, Uchiyama M, et al. Neoadjuvant chemotherapy with mitomycin C, etoposide, and cisplatin for adenocarcinoma of the cervix. *Gynecol Oncol.* 1998; 70:236-40.
96. Thigpen JT, Blessing JA, Fowler WC Jr. Phase II trials of cisplatin as single agents in the treatment of advanced or recurrent non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. *Cancer Treat Rep.* 1986;70:1097-100.
97. Umesaki N, Izumi R, Fushiki H, Hasegawa K, Kono I, Nishida M, et al. Cervical adenocarcinoma, a novel combination chemotherapy with mitomycin C, etoposide, and cisplatin for advanced or recurrent disease. *Gynecol Oncol.* 1999;75:142-4.
98. Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med.* 2014;20:734-43.
99. Barillot I, Horiot JC, Maingon P, Truc G, Chaplain G, Comte J, et al. Impact on treatment outcome and late effects of customized treatment planning in cervix carcinomas: Baseline results to compare new strategies. *Int J Radiat Oncol Biol Phys.* 2000;48:189–200.

References

100. Van der Zee J, Gonzalez Gonzalez D, Van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomised, multicentre trial. *Lancet*. 2000;355:1119–25.
101. Zunino S, Rosato O, Luciano S, Jauregui E, Rossi L, Venencia D. Anatomic study of the pelvis in carcinoma of the uterine cervix as related to the box technique. *Int J Radiat Oncol Biol Phys*. 1999;44:53–59.
102. Ozsarlak O, Tjalma W, Schepens E, Corthouts B, Op de Beeck B, Van Marck E, et al. The correlation of preoperative CT, MR imaging, and clinical staging (FIGO) with histopathology findings in primary cervical carcinoma. *Eur Radiol*. 2003;3:2338–45.
103. Miller TR, Grisby PW. Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. *Int J Radiat Oncol Biol Phys*. 2002;53:353–9.
104. Bipat S, Glas AS, Van der Velden J, Zwinderman AH, Bossuyt PM, Stoker J. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: A systematic review. *Gynecol Oncol*. 2003;91:59–66.
105. Mayr NA, Magnotta VA, Ehrhardt JC, Wheeler JA, Sorosky JI, Wen BC, et al. Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1996;35:915–24.
106. Vincens E, Balleyguier C, Rey A, Uzan C, Zareski E, Gouy S, et al. Accuracy of magnetic resonance imaging in predicting residual disease in patients treated for stage IB2/II cervical carcinoma with chemoradiation therapy : correlation of radiologic findings with surgicopathologic results. *Cancer*. 2008;113:2158–65.
107. Roeske JC, Lujan A, Rotmensch J, Waggoner SE, Yamada D, Mundt AJ. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2000;48:1613–21.
108. Heron DE, Gerszten K, Selvaraj RN, King GC, Sonnik D, Gallion H, et al. Conventional 3D conformal versus intensity-modulated radiotherapy for adjuvant treatment of gynecologic malignancies: A comparative dosimetric study of dose-volume histograms. *Gynecol Oncol*. 2003;91:39–45.
109. Gerszten K1, Colonello K, Heron DE, Lalonde RJ, Fitian ID, Comerci JT, et al. Feasibility of concurrent cisplatin and extended field radiation therapy (EFRT) using intensity-modulated radiotherapy (IMRT) for carcinoma of the cervix. *Gynecol Oncol*. 2006;102:182–8.
110. Roeske JC1, Bonta D, Mell LK, Lujan AE, Mundt AJ. A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. *Radiother Oncol*. 2003;69:201–7.

References

111. Ahamad A1, D'Souza W, Salehpour M, Iyer R, Tucker SL, Jhingran A, et al. Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size. *Int J Radiat Oncol Biol Phys.* 2005;62:1117–24.
112. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys.* 2003;56:1354–60.
113. Viani GA, Manta GB, Stefano EJ, de Fendi LI. Brachytherapy for cervix cancer: low-dose rate or high-dose rate brachytherapy – a meta-analysis of clinical trials. *Exp Clin Cancer Res J.* 2009;28:47-59.
114. Syed AM, Puthawala AA, Abdelaziz NN, El-Naggar M, Disaia P, Berman M, et al. Long-term results of low-dose-rate interstitial-intracavitary brachytherapy in the treatment of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2002;54:67-78.
115. International Commission on Radiation Units and Measurements (ICRU). Dose and volume specification for reporting intracavitary therapy in gynecology. ICRU Report 38. Bethesda, MD: ICRU; 1985..
116. Pelloski CE, Palmer M, Chronowski GM, Jhingran A, Horton J, Eifel PJ. Comparison between CT based volumetric calculations and ICRU reference-point estimates of radiation doses delivered to bladder and rectum during intracavitary radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2005;62:131–7.
117. Haie-Meder C, Potter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiotherapy & Oncology.* 2005 ;74:235–45.
118. Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy radiation physics,radiobiology. *Radiotherapy & Oncology.* 2006;78:67–77.
119. Common toxicity criteria manual, version 4.0. Bethesda, MD: Division of Cancer Treatment, National Cancer Institute 2009.
120. Dimopoulos J, Lang S, Kirisits C. Dose-Volume Histogram Parameters and Local Tumor Control in Magnetic Resonance Image-Guided Cervical Cancer Brachytherapy. *Int J Radiat Oncol Biol Phys.* 2009; 16:22-30.
121. Denekamp J, Bartelink H, Rubin P. Correction for the use of the SOMA LENT tables. American and European LENT Working Committees. *Radiother Oncol.* 1995; 39:191.

References

122. Pötter R, Georg P, Dimopoulos JC, Grimm M, Berger D, Nesvacil N, Georg D, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol.* 2011;100:116-23.
123. From Zubrod CG, Schneiderman M, Frei E. Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chron Dis.* 1960; 11:7-33.
124. International Commission on Radiation Units and Measurements. ICRU report 50: Prescribing, recording and reporting photon beam therapy. ICRU report. Bethesda: International Commission on Radiation Units and Measurements; 1993.
125. Mock U, Dieckmann K, Wolff U, Pötter R. Portal Imaging based definition of the planning target volume during pelvic irradiation for gynecologic malignancies. *Int J Rad Oncol Biol Phys.* 1999;45:227–32.
126. Gerstner N1, Wachter S, Knocke TH, Fellner C, Wambersie A, Pötter R. The benefit of beam's eye view based 3D treatment planning for cervical cancer. *Radiother Oncol.* 1999;51:71-80.
127. Pötter R1, Knocke TH, Fellner C, Baldass M, Reinthaller A, Kucera H Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993-1997) compared to the preceding period in the context of ICRU 38 recommendations.. *Cancer Radiother.* 2000;4: 159-72.
128. Arbyn M1, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F, et al. Worldwide burden of cervical cancer in 2008. *Ann Oncol.* 2011;22 :2675-86.
129. Dey S1, Hablas A, Seifeldin IA, Ismail K, Ramadan M, El-Hamzawy H, et al. Urban-rural differences of gynaecological malignancies in Egypt (1999-2002). *BJOG.* 2010;117:348-55.
130. Shaltout MF, Sallam HN, AbouSeeda M, Moiety F, Hemeda H, Ibrahim A, et al . Prevalence and type distribution of human papilloma virus among women older than 18 years in Egypt: a multicenter, observational study. *Int J Infect Dis.* 2014;29:226-31.
131. Eifel PJ. Chemoradiotherapy in the treatment of cervical cancer. *Seminars in Radiation Oncology.* 2006 ;16:177–85
132. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med.* 1999;340:1144 –53.
133. Mundt AJ, Lujan AE, Rotmensch J, Waggoner SE, Yamada SD, Fleming G, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 2002;52:1330 –7.

References

134. Portelance L, Clifford Chao KS, Grigsby PW, Bennet H, Low D.. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses inpatients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Rad Oncol Biol Phys.* 2001;51:261–6.
135. Chen LA, Kim J, Boucher K, Terakedis B, Williams B, Nickman NA, et al. Toxicity and cost-effectiveness analysis of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for postoperative treatment of gynecologic cancer. *Gynecol Oncol.* 2015;90:1637-40.
136. Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. *Int J Radiat Oncol Biol Phys.* 2013;87:542-8.
137. Chen MF, Tseng CJ, Tseng CC, Kuo YC, Yu CY, Chen WC. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007;67:1438-44.
138. Du XL, Tao J, Sheng XG, Lu CH, Yu H, Wang C, et al. Intensity-modulated radiation therapy for advanced cervical cancer: a comparison of dosimetric and clinical outcomes with conventional radiotherapy. *Gynecol Oncol.* 2012;125:151-7.
139. Mundt AJ, Roeske JC, Lujan AE, Yamada SD, Waggoner SE, Fleming G, et al. . Initial clinical experience with intensity-modulated whole-pelvis radiation therapy in women with gynecologic malignancies. *Gynecol Oncol.* 2001;82:456–63.
140. Georg P, Georg D, Hillbrand M, Kirisits C, Pötter R. Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies. *Radiother Oncol.* 2006;80:19-26.
141. Shin KH, Kim TH, Cho JK, , Kim JY, Park SY, Park SY, et al. CT-guided intracavitary radiotherapy for cervical cancer: Comparison of conventional point A plan with clinical target volume-based three-dimensional plan using dose-volume parameters.. *Int J Radiat Oncol Biol Phys.* 2006;64:197-204.
142. Viswanathan AN, Dimopoulos J, Kirisits C, Berger D, Pötter R.. Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys.* 2007; 68:491-8.
143. Eskander RN, Scanderbeg D, Saenz CC, Brown M, Yashar C. Comparison of computed tomography and magnetic resonance imaging in cervical cancer brachytherapy target and normal tissue contouring. *Int J Gynecol Cancer.* 2010;20:47-53.

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الملخص العربي

سرطان عنق الرحم هو ثالث أكثر أنواع السرطان شيوعاً بين النساء في جميع أنحاء العالم. العلاج الإشعاعي الموضعي، بالتزامن مع الإشعاع الخارجي والعلاج الكيميائي، هو العلاج لسرطان عنق الرحم المتقدمة موضعياً. العلاج الإشعاعي في الحوض كله يؤدي إلى تعرض كميات كبيرة من الأمعاء الدقيقة والغليظة والمستقيم والمثانة. ولذلك، أعراض سمية الجهاز الهضمي والبولي التناسلي الحادة والمزمنة هي من بين الأكثر أهمية في هؤلاء المرضى.

لتحسين الآثار الجانبية للعلاج، تعمل التقنيات المتقدمة على السماح بتقديم جرعات كافية لكلا الورم ومناطق التصريف للمفاوي، بينما في الوقت نفسه تتجنب الأنسجة الطبيعية. العلاج الإشعاعي ثلاثي الأبعاد، وكذلك العلاج الإشعاعي متغير الشدة تضمن تحسن بوضوح في الجرعات إلى الورم المستهدف دون زيادة الجرعة إلى الأجهزة الحيوية.

شملت هذه الدراسة ٤٥ مريضة تعانين من سرطان عنق الرحم المتقدم موضعياً الثلاثي تم علاجهن في قسم العلاج الإشعاعي، جامعة فيينا الطبية. تم تقسيم المرضى في هذه الدراسة إلى مجموعتين. وتضمنت المجموعة الأولى (المجموعة العلاجية) ٣٠ مريضة، والمجموعة الثانية (مجموعة التصوير) وشملت ١٥ مريضة من المصابات بسرطان عنق الرحم المتقدم موضعياً.

وكان الغرض من هذه الدراسة تسجيل النتائج الإكلينيكية باستخدام العلاج الإشعاعي متغير الشدة لعلاج سرطان عنق الرحم المتقدم المحلي، ومقارنتها مع العلاج الإشعاعي ثلاثي الأبعاد من حيث السمية الحادة والمزمنة. وعليه فقد تم تقسيم المجموعة الأولى إلى مجموعتين فرعيتين على حسب طريقة العلاج الإشعاعي الخارجي كالتالي:

المجموعة الفرعية (أ-١): شملت ١٥ مريضة تعانين من سرطان عنق الرحم المتقدم موضعياً وتم علاجهن بواسطة علاج الحوض بواسطة الإشعاع ثلاثي الأبعاد يليه العلاج الإشعاعي الموضعي الموجه.

المجموعة الفرعية (أ-٢): شملت ١٥ مريضة تعانين من سرطان عنق الرحم المتقدم موضعياً وتم علاجهن بواسطة علاج الحوض بواسطة الإشعاع متغير الشدة يليه العلاج الإشعاعي الموضعي الموجه.

معظم المرضى عانين السمية الحادة الخفيفة والتي لم تستوجب إيقاف العلاج. وعلاوة على ذلك، كانت الأعراض الجانبية الناتجة عن العلاج الإشعاعي متغير الشدة أقل كثيراً من تلك الناتجة عن العلاج الإشعاعي ثلاثي الأبعاد. كانت هناك نسبة أعلى من سمية الجهاز الهضمي الحادة في المرضى الذين عولجوا بواسطة العلاج الإشعاعي ثلاثي الأبعاد مما كان عليه في العلاج الإشعاعي متغير الشدة. كان الإسهال أكثر مضاعفات الجهاز الهضمي شيوعاً. الإسهال والام في البطن حدثاً في ٣.٧٣٪ و ٤٠٪ من المرضى من مجموعة (أ-١) مقابل ٦٠٪ و ١٣٪ من مجموعة (أ-٢) على التوالي.

كان معدل الدرجة الثانية من سمية الجهاز الهضمي أقل في مجموعة العلاج الإشعاعي متغير الشدة وكذلك قل معدل استخدام الأدوية مضادة الإسهال. كذلك حدثت سمية الجهاز الهضمي المتأخرة بصورة أكثر كثافة في المرضى الذين تم علاجهم بواسطة العلاج الإشعاعي ثلاثي الأبعاد حيث عانى ٦٠٪ من مرضى المجموعة (أ-١) من سمية الجهاز الهضمي في مقابل ٤٦.٧٪ في المجموعة (أ-٢). عانت مريضة واحدة فقط من المجموعة (أ-٢) من سمية الجهاز الهضمي المتأخرة الشديدة حيث كانت تعاني من ناسور مستقيمي مهيلي.

وذكر الشيء نفسه بالنسبة لسمية الجهاز البولوي التناسلي حيث كانت جميع الأعراض البولوية التناسلية الحادة أعلى كثيراً في المرضى الذين تلقوا العلاج الإشعاعي ثلاثي الأبعاد مقارنة مع المرضى تلقى العلاج الإشعاعي متغير الشدة. وكانت أكثر الأعراض شيوعاً هو تواتر التبول حيث تم تسجيل الدرجة الثانية منه في ٢٠٪ و ٦٠٪ من مرضى المجموعتين A1 و A2 على التوالي. كما تم تسجيل البيلة البولوية من الدرجة الأولى في ٢٦.٧٪ من مرضى المجموعة (أ-١) و في ٦.٧٪ من مرضى المجموعة (أ-٢).

أظهرت نتائج الدراسة الحالية أن تقليل الحجم من أنسجة الأمعاء الدقيقة والمستقيم والمثانة البولوية والتي تتعرض للجرعة القسوى من الإشعاع ينتج عنه انخفاض ملحوظ في أعراض سمية الجهازين الهضمي والبولوي التناسلي. في هذه الدراسة، كان هناك انخفاض ذو دلالة إحصائية في حجم الأمعاء الدقيقة التي تلقت جرعة إشعاعية

عالية حيث كانت جرعة العلاج الإشعاعي المتوسط التي تلقتها الأمعاء الدقيقة في المرضى الذين تلقوا العلاج الإشعاعي متغير الشدة 27.16 ± 1.43 غراي في مقابل 1.07 ± 1.33 غراي في مجموعة العلاج الإشعاعي ثلاثي الأبعاد.

كان هناك أيضاً انخفاض ذو دلالة إحصائية في متوسط جرعة الإشعاع التي تلقاها المستقيم في مرضى المجموعة (أ-1) عن مرضى المجموعة (أ-2). وعلى النقيض، فقد تلقت المثانة البولية جرعة أكبر في المجموعة (أ-2).

هذا وقد قيمت هذه الدراسة طريقتين من طرق تحديد الورم المستهدف أثناء العلاج الموضعي لسرطان عنق الرحم إما عن طريق الأشعة المقطعية أو الرنين المغناطيسي. وقد أظهرت المقارنة بين الطريقتين أن الحجم الورم المحدد بواسطة الأشعة المقطعية كان أكبر من المحدد بواسطة الرنين المغناطيسي.



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رسالة مقدمة

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ضمن متطلبات درجة

الدكتوراه

في

علاج الأورام والطب النووي

من

نعمات السيد السيد حجازي
بكالوريوس الطب والجراحة، ٢٠٠٢
ماجستير العلاج الإشعاعي، ٢٠٠٨
كلية الطب، جامعة الإسكندرية

[٢٠١٥]



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رسالة مقدمة من

نعمات السيد السيد حجازى

للحصول على درجة

الدكتوراه

فى

علاج الأورام والطب النووي

التوقيع

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