Gynecologic Oncology Reports 52 (2024) 101362

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Upfront boost to gross disease followed by elective pelvic radiation improves compliance to radiation therapy delivery metrics in locally advanced vulvar cancer

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ARTICLE INFO

Keywords:
Locally advanced cancer of the vulva
Radiation therapy
Chemotherapy
Combined modality therapy
Overall treatment time

ABSTRACT

Locally advanced cancer of the vulva (LACV) is commonly diagnosed in older women (>65 years), and is treated using combined multimodality therapy (CMT) that includes radiation therapy (RT). Compliance to optimal RT metrics, including completion of > 20 fractions, overall treatment duration of < 8 weeks (56 days), and < 1 week intra-treatment break is associated with better disease outcomes. However, published results note that a significant number of patients with LACV do not adhere to these metrics. The aim of our study is to evaluate whether a modified sequence of RT delivery, treating the localized boost volume upfront followed by the larger elective nodal volume is associated with improved compliance to optimal RT delivery metrics.

1. Introduction

Annually, an estimated 6,470 new cases of cancer of the vulva are diagnosed, and account for approximately 6 % of all gynecologic malignancies. (National Cancer Institute. Cancer Stat Facts: Vulvar Cancer; Medical Report; National Cancer Institute: Rockville, MD, USA, December 26, 2023; Surveillance, 2022) The median age at diagnosis is 69 years (range 65 to 74 years). At presentation, approximately 40 % have locally advanced cancer of the vulva (LACV) with extension to surrounding structures and/or metastases to regional lymph nodes. (National Cancer Institute. Cancer Stat Facts: Vulvar Cancer; Medical Report; National Cancer Institute: Rockville, MD, USA, December 26, 2023; Surveillance, 2022) As per clinical studies in vulvar cancer and the National Comprehensive Cancer Network (NCCN) treatment guidelines, (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Vulva version 2. https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf, 2022; Moore et al., 2012; Rao et al., 2017) combined modality therapy (CMT) is recommended for treating LACV. Administering multimodality therapy in older patients with comorbidities and associated frailty is challenging. (Gadducci and Aletti, 2020; Stuckey et al., 2013).

Similar to cancer of the cervix, (National Comprehensive Cancer Network Clinical Practic Guidelines in Oncology, Cervix version 1, https://www.nccn.org/guidelines/guidelines-detailcategory=1id=, 2021; Song et al., 2013; Ohri et al., 2016) the clinical significance of radiation therapy (RT) delivery metrics in treatment of cancer of the vulva are reported. (Swanick et al., 2017; Ashmore et al., 2021; Nguyen et al., 2022) However, unlike cervical cancer most women diagnosed with vulvar cancer are much older with associated multiple comorbidities. Compliance to optimal RT delivery parameters is known to result in improved overall survival. Swanick et al (Swanick et al., 2017) and Ashmore et al (Ashmore et al., 2021) described impact of RT delivery in the setting of adjuvant treatment. The three identified optimal RT delivery metrics include > 20 treatment fractions, overall treatment time (OTT) < 8 weeks, and < 1 week treatment break. Similarly, in patients with LACV, Nguyen et al (Nguyen et al., 2022) reported the favorable impact of < 7 day treatment break on disease outcomes in the setting of primary RT alone or CMT.

These observations raise important considerations for RT delivery parameters with/without chemotherapy in the treatment of cancer of the vulva. Given advances in surgical techniques, (Wagner et al., 2022) radiation technology (Rao et al., 2017; Rao et al., 2017; Gaffney et al., 2016) and the evolving role of biology (Lee et al., 2016), our contemporary practice needs to pursue strategies that may further improve compliance to optimal RT delivery for this disease. One such approach would be to refine the RT schema for dose delivery. Traditionally, a large

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https://doi.org/10.1016/j.gore.2024.101362
Received 26 January 2024; Received in revised form 4 March 2024; Accepted 5 March 2024
Available online 6 March 2024

field encompassing the elective lymph nodes and the involved primary site is irradiated upfront, followed by a boost to the gross disease only. More recently, the simultaneous integrated boost (SIB) technique has been used to treat the gross disease and elective nodal sites at the same time with the gross disease receiving a higher dose per fraction than the elective regions.

We describe an alternate flipped RT schema, which is risk-tailored, such that the highest-risk volume of disease i.e. primary + involved nodes are treated upfront, followed by the larger elective nodal volume that includes the primary, bilateral inguinal and pelvic nodes. We reasoned that by using the flipped sequence, the RT dose delivered would be similar to traditional RT plans that deliver pelvic RT followed by boost or using SIB. Furthermore, by integrating a lag in treatment of the larger elective nodal volume, we might mitigate the onset of acute hematologic, gastrointestinal, and genitourinary toxicity early in the treatment course resulting in overall better tolerance to RT/CMT with less intra-treatment break.

2. Clinical cases

In this retrospective IRB approved study, we review our experience treating women over the age of 70 years using the flipped RT sequence. We treated 4 patients diagnosed with LACV between 9/2019 to 10/2021 $\geq$ 70 years of age. All four patients were ambulatory with ECOG performance status 0–1, median age 79 years (range: 73 years −88 years), and FIGO stage II- IIIB. Three patients were treated with concurrent weekly cisplatin + RT, and one patient received adjuvant RT alone because the patient refused chemo. Table 1.

Table 2 summarizes the treatment parameters. IMRT plans were used to deliver the flipped RT sequence with upfront boost followed by the elective pelvic field. The total RT dose, dose/ fraction prescribed was at the discretion of the treating physician. The upfront boost dose to the primary and positive inguinal nodes ranged from 1260 cGy to 2400 cGy. The composite total RT dose/ fractions to the gross disease ranged from 5760 cGy/32 fractions to 6480 cGy/36 fractions, and dose to elective pelvic nodal volume ranged from 3600 cGy to 4500 cGy. The RT course was delivered over an average of 58 elapsed days [range: 44 to 69 days]. The average intra-treatment break was 5 days [range: 4 to 6 days]. Three patients received concurrent weekly cisplatin and completed $\geq$ 5 doses (two patients received 6 doses, and one patient received 5 doses).

All patients experienced radiation treatment related grade 2 gastrointestinal (GI) toxicity, grade 1 genitourinary (GU) symptoms, and 3 patients experienced moist skin desquamation in the area of the boost field during treatment that did not require a protracted treatment break. Three patients received $\geq$ 5 weekly doses of cisplatin; all had grade 1–2 hematologic toxicity. Table 3 summarizes the clinical response scored at follow up within 12 weeks after treatment.

3. Discussion

Several clinically significant RT delivery metrics in treatment of gynecologic cancers are identified, which include RT dose/ fractionation, intra-treatment interruptions, and overall treatment time (OTT). Available contemporary data also illustrate that compliance to RT delivery metrics in treatment of cancer of the vulva directly impacts disease outcomes.

The SEER-Medicare linked population based study (Swanick et al., 2017) examined RT use in 444 women age $\geq$ 66 years with node positive vulvar cancer. The study evaluated outcomes by pre-defined adjuvant RT delivery metrics i.e. completion of $\geq$ 20 RT fractions, RT treatment duration < 8 weeks, and < 1 week intra-treatment break. The results identified a combined variable of three optimal RT delivery parameters (number of fractions, treatment breaks, and OTT) to be associated with improved disease outcomes. Patients meeting all three RT delivery metrics had better overall survival (OS) ($p = 0.001$), and cancer-specific survival (CSS) ($p = 0.005$) compared to surgery alone. Furthermore, patients that failed to adhere to these three metrics demonstrated only marginal improvement in disease outcomes compared to surgery alone. In multivariate analysis, the strongest covariate independently predicting compliance to optimal RT delivery was use of IMRT ($p = 0.002$).With chemotherapy patients were less likely to meet the optimal metrics ($p = 0.04$).

In this population-based study (Swanick et al., 2017) remarkably, only 51 % of patients were able to receive RT compliant with all three metrics, and only 67 % of patients received $\geq$ 20 fractions. This is in contrast, to the randomized RT arm of Gynecologic Oncology Group (GOG) 37 study, where 90 % of patients completed RT without modification. (Kunos et al., 2009) This observation reflects differences between a tightly screened patient population enrolled in clinical trials and those diagnosis and clinical outcomes in real world population setting.

The study reported by Nguyen et al (Nguyen et al., 2022) includes only LACV patients (FIGO stage II- IV) identified from the 2004–2017 NCDB database on vulvar cancer. Among these cases, 72.29 % had stage III or IVA disease. Patients were stratified by type of treatment, 856 received RT, and 1522 received CMT. The median age was 67 years (range 56–78 years), and median dose of total radiation was 5720 cGy (IQR 5040–6300). The delay in completion of RT was categorized into two groups < 7 days or $\geq$ 7 days. Completion of RT with < 7 days delay was associated with improved OS, and was independent of administration of concurrent chemotherapy. In the RT only treated group, the median OS in patients with < 7 days and $\geq$ 7 days treatment delay was 34.9 versus 21.6 months ($p < 0.01$), respectively. In CMT treated patients, the median OS in patients with < 7 days and $\geq$ 7 days treatment delay was 58 versus 41.3 months ($p < 0.01$), respectively. On multivariate subset analysis, both RT and CMT treated patients showed improved OS when treatment was completed with < 7 days delay vs $\geq$ 7 days delay, and was independent of the administration of concurrent chemotherapy.

Our early experience with the flipped RT schema delivering upfront boost followed by elective nodal RT in older ($\geq$70 years) women with LACV signals excellent compliance to optimal RT delivery metrics. The patients in this review received 32 to 36 RT fractions exceeding the metric of > 20 EBRT fractions, RT was delivered on average over 58 elapsed days [range: 44 days to 69 days] approaching the optimal metric of 8 weeks, and no patients had $\geq$ 7 days [ranged from 4 days to 6 days] intra-treatment break. We also observed that concomitant delivery of weekly cisplatin with RT was well tolerated.

The Dutch phase II study (van Triest et al., 2021) on definitive chemo-radiation treatment for LACV used concomitant capecitabine and RT. In this trial, RT was delivered using a flipped sequence with upfront boost and planned lag in starting the elective pelvic field without scheduled treatment break. Although capecitabine is not the preferred drug for treating vulvar cancer in US, the high rates (90 %) of compliance in completing RT per protocol is noteworthy. This is similar to our study where patients receiving cisplatin concurrently with the flipped RT sequence were able to complete RT without significant delay.

Table 1
Patient characteristics.

Patients	Age (years)	ECOG PS	FIGO Stage	Histology	Treatment
1	79	0	IIIB	SCC	CMT
2	76	0	IB	SCC	CMT
3	73	0	IIIA	SCC	S + RT
4	88	1	II	SCC	CMT

CMT: combine modality therapy; SCC: squamous cell cancer; S + RT: surgery plus radiation therapy.

4. Summary and conclusion

Our early experience using the flipped RT schema, delivering upfront

Table 2
Treatment characteristics including RT dose, fractionation, and overall treatment duration with intra-treatment break.

Patient	Treatment plan	Cisplatin doses	Upfront RT boost dose/ dose per fraction to primary tumor and positive inguinal nodes	RT dose/ dose per fraction to elective pelvic nodal volume	Composite RT total dose / No: of fractions	Elapsed days (overall treatment time)	Intra- treatment break (days)
1	CMT	6	1980 cGy/180 cGy	3960 cGy/180 cGy	5940 cGy/33	51	4
2	CMT	5	1980 cGy/180 cGy	4500 cGy/180 cGy	6480 cGy/36	69	5
3	S + RT	NA	1260 cGy/180 cGy	4500 cGy/180 cGy	5760 cGy/32	69	6
4	CMT	6	2400 cGy/200 cGy	3600 cGy/180 cGy	6000 cGy 32	44	5

CMT: combine modality therapy; cGy: Centigray.

Table 3
Response at completion of therapy.

Patent	FIGO Stage at diagnosis	Treatment plan	Disease status at completion of therapy
1	IIIB	CMT	CR
2	IB	CMT	CR
3	IIIA	S + RT	CR
4	II	CMT	PR

CMT: combine modality therapy; CR: clinical complete response; PR: partial response; S + RT: surgery plus radiation therapy.

boost followed by elective nodal RT suggests good compliance to identified optimal RT delivery metrics for gynecologic malignancies. Additionally, patients receiving concomitant chemotherapy were able to receive 5–6 weekly doses of concomitant cisplatin.

The high prevalence of vulvar cancer in patients with advanced age and comorbidities is particularly challenging. Further study on a larger population of patients is warranted for providing a comparative assessment of compliance to delivery metrics observed when using the more commonly used large elective field upfront and the flipped schedule encompassing risk-tailored volume of boost upfront followed by elective field RT. Such a study would help establish optimal sequencing of radiation in treatment of vulvar cancer. There remains an unmet need for conducting prospective clinical trials aimed at optimizing treatment delivery in patients with LACV. The low incidence of vulvar cancer underscores the need to establish collaborations through cooperative national group effort for completing such prospective studies.

Funding

NA.

Conflict of Interest: KZ receives funding from AstraZeneca. The remaining authors declare no conflict of interest.

Author contribution: Conceptualization: M.C., T.S., V.G., and V.K.
Writing: original draft preparation: M.C., T.S., and M. L.
Writing: review and editing, all authors.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to acknowledge the data management support provided by Ms. Carol White.

References

Ashmore, S., Crafton, S.M., Miller, E.M., et al., 2021. Optimal overall treatment time for adjuvant therapy for completely resected, node-positive vulvar cancer. Gynecol. Oncol. 161 (1), 63–69.
Gadducci, A., Aletti, G.D., 2020. Locally advanced squamous cell carcinoma of the vulva: a challenging question for gynecologic oncologists. Gynecol. Oncol. 158, 208–217.
Gaffney, D.K., King, B., Viswanathan, A.N., et al., 2016. Consensus recommendations for radiation therapy contouring and treatment of vulvar carcinoma. Int J Radiat Oncol Biol Phys. 95 (4), 1191–1200.
Kunos, C., Simpkins, F., Gibbons, H., et al., 2009. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol. 114, 537–546.
Lee, L.J., Howitt, B., Catalano, P., et al., 2016. Prognostic importance of human papillomavirus (HPV) and p16 positivity in squamous cell carcinoma of the vulva treated with radiotherapy. Gynecol. Oncol. 142, 293–298.
Moore, D.H., Ali, S., Koh, W.J., et al., 2012. A phase II trial of radiation therapy with cisplatin chemotherapy for treatment of locally advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. Gynecol. Oncol. 124 (3), 529–533.
National Cancer Institute. Cancer Stat Facts: Vulvar Cancer; Medical Report; National Cancer Institute: Rockville, MD, USA, December 26, 2023. https://seer.cancer.gov.
National Comprehensive Cancer Network Clinical Practic Guidelines in Oncology, Cervix version 1, https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1426 2021 Last accessed May 25, 2021.
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Vulva version 2. https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf 2022 (Last accessed February 21, 2022).
Nguyen, N.T., Zhao, X., Ponzini, M., et al., 2022. Time to completion of radiation treatment in LAVC and the impact on survival. Gynecol Oncol. 167, 159–166.
Ohri, N., Rapkin, B.D., Guha, C., et al., 2016. Radiation therapy noncompliance and clinical outcomes in an urban academic cancer center. Int. J. Radiat. Oncol. Biol. Phys. 95 (2), 563–570.
Rao, Y.J., Chundury, A., Schwarz, J.K., Hassanzadeh, C., DeWees, T., Mullen, D., Powell, M.A., Mutch, D.G., Grigsby, P.W., 2017. Intensity modulated radiation therapy for squamous cell carcinoma of the vulva: treatment technique and outcomes. Adv. Radiat. Oncol. 2, 148–158.
Rao, Y.J., Chin, R., Hui, C., et al., 2017. Improved survival with definitive chemoradiation compared to definitive radiation alone in squamous cell carcinoma of the vulva: a review of the National Cancer Database. Gynecol. Oncol. 146 (3), 572–579.
Song, S., Rudra, S., Hasselle, M.D., et al., 2013. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. Cancer. 119 (2), 325–331.
Stuckey, A., Schutzer, M., Rizack, T., et al., 2013. Locally advanced vulvar cancer in elderly women: is chemoradiation beneficial? Am J Clin Oncol 36, 279–282.
Surveillance, 2022. Epidemiology and end results program. Last accessed February 21).] National Cancer Institute. https://seer.cancer.gov/statfacts/html/vulva.html.
Swanick, C.W., Eifel, P.J., Huo, J., et al., 2017. Challenges to delivery and effectiveness of adjuvant radiation therapy in elderly patients with node-positive vulvar cancer. Gynecol Oncol. 146 (1), 87–93.
van Triest, B., Rasing, M., van der Velden, et al., 2021. Phase II study of definitive chemoradiation for locally advanced squamous cell cancer of the vulva: an efficacy study. Gynecol Oncol. 163, 117–124.
Wagner, M.M., van der Zee, A.G.J., Oonk, M.H.M., 2022. History and updates of the GROINSS-V studies. Cancers. 14, 195.