Case Reports in Oncology

Case Rep Oncol 2021;14:1010–1018
DOI: 10.1159/000517022
Received: May 4, 2021
Accepted: May 4, 2021
Published online: June 28, 2021

Case Report

Role of Radiotherapy in Recurrent Intra-Abdominal Yolk Sac Tumor

Marhendra Satria Utama[a] Andi Kurniadi[b] A.A. Citra Yunda Prahastiwi[c] Antony A. Adibrata[d]

[a]Radiation Oncology Sub Division, Department of Radiology, Hasan Sadikin General Hospital, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia; [b]Gynecology Oncology Sub Division, Department of Obstetrics and Gynecology, Hasan Sadikin General Hospital, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia; [c]Radiation Oncology Division, Cancer Center, Santosa Hospital Bandung Kopo, Bandung, Indonesia; [d]Medical Education Program, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

Keywords
Yolk sac tumor · Curative · Radiation dose · 3D-CRT · Recurrent case

Abstract
Yolk sac tumor (YST) is a rare malignant germ cell tumor with no appropriate treatment strategy to date. However, patients are treated on a case-to-case basis as per various case reports that have been published. Here, we present a case of 27-year-old female patient who presented to us with chief complaints of severe abdominal pain associated with leucorrhea. She previously had a similar pain episode, which was then evaluated by a multidisciplinary team. She was diagnosed with YST. After that, she underwent 6 cycles of chemotherapy, but there was no improvement. Then the medical oncologist referred her to performed radiotherapy. Then, the radiation oncologist decided to give her curative radiotherapy of 3D-CRT. After completing her sessions, she felt better and clinically improving. After that, she was discharged and scheduled a follow-up visit for first evaluation. At her follow-up visit, she was feeling well, and we decided to have an abdominal MRI.

Introduction

Germ cell tumors are growths that form from reproductive cells. They can be benign or malignant. Most cancerous germ cell tumors arise as cancers of the testicles or the ovaries. Germ cell tumors could occur in other body areas than the testicles and ovaries (extragonadal

Correspondence to:
Marhendra Satria Utama, marhendra@unpad.ac.id

germ cell tumors), such as the abdomen, brain, and thorax, though it is infrequent and still not clear why.

A yolk sac tumor (YST) is a malignant germ cell tumor. It typically occurs in the gonads and rarely occurs as an extragonadal germ cell tumor. It predominantly occurs in girls and women of childbearing age. That is why fertility preservation is particularly essential. Before the recent advancements in treatment strategies, the yolk cell tumor prognosis was very poor [1].

In advance of the advent of combination chemotherapy, the prognosis of YST patients was poor, with an average 80–90% mortality rate within 2 years of diagnosis [1]. By the late 1970s, the YST's prognosis had improved due to novel chemotherapeutic regimens. In the 1990s, combination of substances bleomycin, etoposide, and cisplatin (BEP) was established to be highly active against malignant germ cell tumors and became the standard treatment for this type of tumor [2]. However, the prognosis for YST remains disappointing. Recent studies have demonstrated FIGO stage and tumor-reductive surgery strongly affect this disease's prognosis [3]. Other prognosis factors remain unclear.

After the advent of the latest chemotherapeutic and radiotherapeutic regimes combined with surgical interventions, the prognosis is better. However, it remains unsatisfactory [4]. While most of the prognostic factors are still unclear, researchers reported that the FIGO stage and tumor-reductive surgery strongly affect the prognosis of disease [2]. Serum α-fetoprotein (AFP) level is one of the yolk cell tumor hallmarks and facilitates its diagnosis. It is useful for monitoring its clinical course and response to treatment [3]. This study presents a case of recurrent YST in the retroperitoneum. Informed consent was already provided and written by the patient and her family.

Case Report

A 27-year-old woman, referred by a medical oncologist, came to the radiotherapy clinic with the chief complaint of abdominal distension with severe abdominal pain along with massive leucorrhea (fluor albus). According to her medical record, in mid-2017, she had an episode of right lower quadrant abdominal pain. She went to the public health center and was given drugs, but there are no changes. Three months later, her condition was getting worse, and the public health center referred her to a gynecologist.

Gynecologist was assembling a tumor meeting board consisting of gynecology oncologist, radiation oncologist, digestive surgeon, and medical oncologist, and the tumor board was concluded that she was diagnosed with suspected YST, afterward they decided to give treatment to her starting with joining surgery between gynecologist and digestive surgeon followed by chemotherapy and radiotherapy.

Her first AFP examination level was high (14,425 ng/mL). Her abdominal ultrasonography was done, and gynecologist found that her leucorrhea was caused by endocervicitis with no sign of endocervical cancer or enlargement on the lymph node and surrounding area, and she was treated with antibiotics. Computed tomography (CT) scan was done and revealed an intra-abdominal solid mass located in the retroperitoneum area with tumor size 24 × 20 × 18 cm (shown in Fig. 1).

She was referred to digestive surgeon, who did the exploratory laparotomy surgery in conjunction with gynecologic surgeon in December 2017 as plan. A tumor resection was performed during the first explorative laparotomy. The histopathology result concluded the intra-abdominal YST, and the serum AFP levels decreased from 14,425 to 5,550.20 ng/mL after surgery was performed.

After that, the surgeon referred her to a hemato-oncologist for chemotherapy, where she was given 6 cycles of BEP chemotherapy regimen consisting of bleomycin (20 mg for 4 consecutive

Case Rep Oncol 2021;14:1010–1018
DOI: 10.1159/000517022

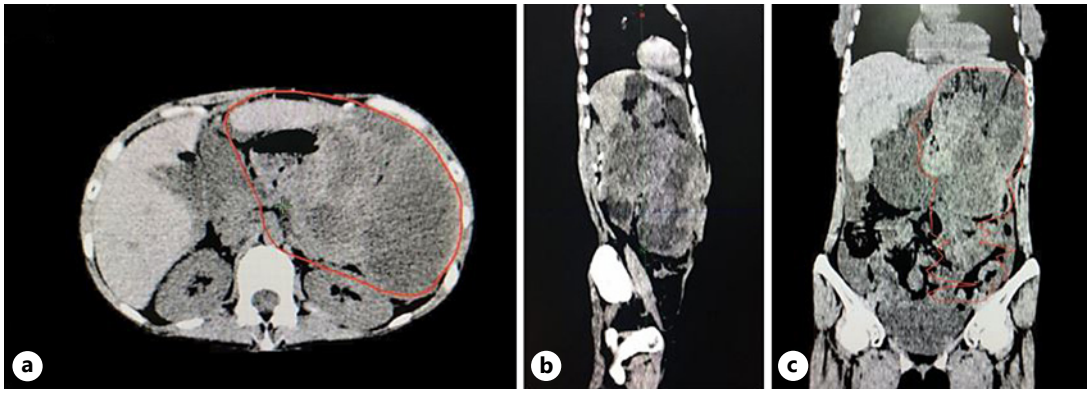

Fig. 1. Abdominal CT-scan (axial section (**a**), sagittal section (**b**), coronal section (**c**)). CT, computed tomography.

days), etoposide (160 mg for 4 consecutive days), and cisplatin (40 mg for 4 consecutive days), the serum AFP levels decreased from 5,550.20 to 825.40 ng/mL, and at that time, the CT scan revealed that the tumor size had significantly reduced, but we cannot show it here because that CT-scan data was lost by patients family.

After the chemotherapy was done, she felt better. However, 4 weeks after the chemotherapy, she felt that her abdomen was getting bigger as twice as usual. She referred back to digestive surgeon, and then the second surgery was performed. It was believed to be the recurrence of the tumor. After the second surgery, the histopathology came up with the same results, and chemotherapy was given back to the patient in 4 cycles. Since there was no response to chemotherapy, and her abdomen was still distended, she got referred by her medical oncologist to a radiation oncologist for further management.

At the time of her admission to radiotherapy department on early February 2018, her physical examination revealed an abdominal distention in right lower quadrant with 18 × 12 × 6 cm in size. She was having abdominal pain of grade 7 intensity associated with nausea and vomiting. Her AFP serum levels were elevated to 15,445.54 ng/mL (normal level, <10 ng/mL); cancer antigen 125 (CA-125) levels were elevated to 151.1 U/mL (normal level, <35 U/mL); the serum β-human chorionic gonadotropin was within normal limit 0.0185 mIU/mL (β-hCG; normal level, <10 mIU/mL); and squamous cell carcinoma antigen were within the normal limits.

She did not have a history of diabetes and hypertension. She had a family history of cancer, her grandmother died because of cervical cancer, and her mom died of liver cancer, and her father died of lung cancer. She was unmarried, health-care management professional by occupation with no history of smoking and alcoholic drink.

So, after assessment was performed, we decided to give her a curative radiotherapy dose. Radiotherapy was performed using 10 megavoltage photons for a total dose of 50 Gy divided into 2 phases. We decided to give her 2-phase radiotherapy because we need to see the radiotherapy responses after curative dose of 30 Gy radiotherapy is delivered, and if the responses are positive, we continued to give her booster dose for another 20 Gy in phase 2. Phase one radiotherapy was given to her in 30 Gy divided by 10 sessions with 3 Gy daily fractionations in 5 days and continued by the second phase with plan 20 Gy divided by 10 sessions with 2 Gy daily dose fractionations in 5 days. Radiotherapy planning was given by field in field 3D-CRT planning because of the large abdominal mass. Figure 2a and b shows the phase 1 and phase 2 radiotherapy planning for this case.

The dose-volume histogram curve relating radiation dose to tissue volume in radiation therapy planning on phase 1 is shown in Figure 3a and on phase 2 is shown in Figure 3b.

Case Rep Oncol 2021;14:1010–1018
DOI: 10.1159/000517022

Fig. 2. 3D-Conformal radiotherapy. Planning phase 1 (**a**), planning phase 2 (**b**).

After the 10th radiotherapy session on phase 1 she felt much better, she already received total 30 Gy on radiotherapy dose, and the size of the tumor reduced significantly from 18 × 12 × 6 to 12 × 8 × 6 cm, because clinically response to the first phase, so we decided to continue to the second phase radiotherapy with total dose 20 Gy in 10 fractionations. However, after the 10th session on phase 2, she complained of severe nausea and vomited badly. So, we prescribed anti-nausea and

Case Rep Oncol 2021;14:1010–1018
DOI: 10.1159/000517022

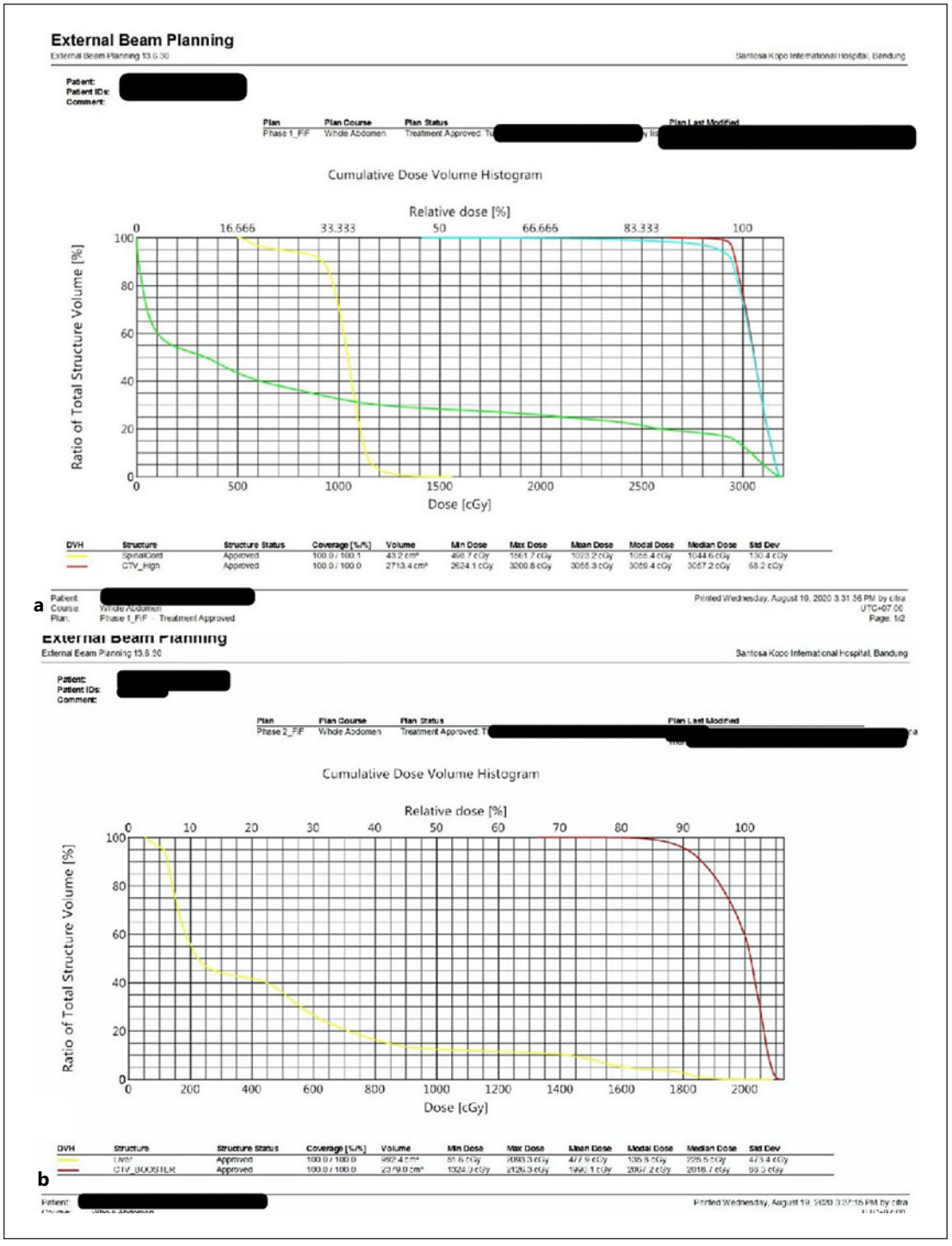

Fig. 3. DVH 3D-CRT radiotherapy planning. On phase 1 (**a**), on phase 2 (**b**). DVH, dose-volume histogram.

anti-emetic for her and she feels better. She was completely relieved of her symptoms after completing her radiotherapy sessions and clinically proved by mass palpation measurement that reduced from 18 × 12 × 6 to 8 × 6 × 6 cm, and there was no pain in the abdomen anymore, the AFP serum levels also decreased from 15,445.54 to 244.41 ng/mL and her fluor albus was also stopped. We scheduled a follow-up visit after 3 months to perform evaluation by MRI.

Case Rep Oncol 2021;14:1010–1018
DOI: 10.1159/000517022

After 3 months, she was feeling well, and we decided to have her abdominal MRI. While she was on her waiting list for an MRI, she came to the ER complaining that her abdominal pain was back again, and shortly after that, she was taken to the ICU because of severe pain in the abdomen. Three days later, she died. Nevertheless, the family was very thankful to the radiotherapy team because they felt that radiotherapy was provided her with so much relief of her symptoms.

Discussion/Conclusion

YST is a rare malignant germ cell tumor. Most of the data published on this topic are in the form of case reports. This is because of the clinical manifestation variation, tumor presentation, CT findings, or treatment approach. With the advancements in the field of oncology, treatment modalities have also been changed with time. Surgical resection, combination chemotherapy, interval debulking, and radiotherapy are common treatment modalities which are frequently used nowadays.

There are several studies about a case of retroperitoneal YST, such as Guo and his colleagues reported that they managed the case with surgical and chemotherapeutic interventions very well. It is considerably difficult to manage these cases; however, complete resection of retroperitoneal tumors is crucial for successful treatment [4]. DiPerna et al. [5] noted that the resection of tumors, which are invading major vascular structures like abdominal aorta, may provide acceptable morbidity and mortality among patients. Fertility sparing is one of the most concerning issues when dealing with the surgical treatment of YST. The reproductive function may be retained by preserving the uterus and the contralateral ovary, regardless of the tumor stage. Cicin et al. [6] observed that fertility-sparing surgery was as effective as radical surgery in patients with ovarian YST. On the other, Peccatori and his companions [7] retrospectively analyzed 129 malignant ovarian germ cell tumor patients found that fertility-sparing surgery did not have any effect for the recurrence or survival rate in ovarian germ cell tumor patients. Similarly, in another study, Ayhan et al. [8] found no significant difference between conservative and nonconservative surgery in recurrence or survival rate of patients. Contrastingly, Zanagnolo et al. [9] noted that fertility-sparing surgery was safe for patients with malignant ovarian germ cell tumors.

The pathogenesis of YST is yet still unknown. The classical theory suggests it happened due to the misplaced of primordial germ cells and create local transformation. At the fourth to the sixth week of embryogenesis, germ cells migrate through the midline dorsal mesentery; a remnant of tissue anywhere along the migration course can be a site of GCT in the future [10]. The histopathological features of YST are distinctive, with proliferation of tubular and papillary structures and sinusoidal formation from fibrovascular cores lined by tumor cells (Schiller-Duval bodies) with frequent mitotic form [11].

Majority of adults with YST mostly present with advanced local disease and distant metastasis, therefore, the complete local excision is rarely feasible. This tumor most commonly spreads to the regional lymph nodes, lung, liver, and bone. Extragonadal germ cell tumors may reach a large size with no or relatively few symptoms [12]. The most presenting symptoms for patients with endodermal primitive tumors are rapidly enlarging pelvic mass and pain [13]. These symptoms presented in our case that her first chief complaint was enlarging abdominal mass along with severe abdominal pain.

In the course of further investigation, our patient was also diagnosed with high AFP levels (the first AFP examination was 14,425 ng/mL) that significantly decreased during the treatment the patient received, after 4 cycles of BEP chemotherapy the AFP serum level was decreasing to 825.40 ng/mL. The decreasing ratio of postoperative AFP serum level is an

Case Rep Oncol 2021;14:1010–1018
DOI: 10.1159/000517022

effective indicator to determine whether residual disease remains after surgery [14]. Response to chemotherapy also can be evaluated by normalization of AFP [14]. According to the literature, in order to detect a relapse, the AFP is more sensitive than the CT scan [12]. Despite its significance, the prognostic value of high levels of AFP in YSTs at the time of diagnosis remains controversial. In two studies AFP >1,000 ng/mL was associated with a higher risk of relapse after treatment [15]. Two other studies found that preoperative serum AFP levels before initial surgery had no significant correlation with the prognosis [14]. Serum AFP levels are excellent marker for the disease burden and severity of the disease. It also shows the response to treatment. In a study, Talerman et al. [16] also stated serial serum AFP may be used as a tool for diagnostic purposes and the detection of metastases and recurrence.

In order to confirm diagnosis morphologically, explorative laparotomy surgery has been made in our case. Laparotomy was recommended in order to achieve an optimal staging and to avoid an uncertain tumor cell spread. Today, advancements in technologies enabled us to achieve the same or even better surgical prognosis and a potentially faster recovery with less traumatic minimally invasive laparoscopic surgery than a conventional laparotomy [17].

Extragonadal germ cell tumors have been managed under the same principle as their primary gonadal counterparts, using the treatment comprised of systemic chemotherapy together with local treatment, including surgery and radiotherapy [18]. The aim of surgery is removing the primary tumor without excessive morbidity. Adjuvant radiotherapy can be considered for patients with extensive intra-abdominal disease when initial debulking surgery is not an option [19]. Furthermore, adjuvant chemotherapy can also be considered for patients with suspected extensive local metastasis. In our case adjuvant chemotherapy was done with 4 BEP cycles was chosen as an option to reduce the tumor size and also to minimize the extent of surgical procedure causing as minimal as possible impact on the patient's fertility. Before the introduction of effective chemotherapy, the prognosis for patients with YST was poor, with a 3-year survival rate of 13% for malignant endodermal primitive tumors. The establishment of BEP chemotherapy for malignant germ cell tumors has significantly improved outcomes. BEP chemotherapy is regarded to be a gold standard regimen for the first-line treatment of germ cell tumors at all disease stages [20].

In our case, the AFP serum level was decreased after radiotherapy, indicated from 15,445.54 to 244.41 ng/mL. This result indicates that radiotherapy is the most effective therapy for our YST patient. If chemotherapy is no longer effective, options to radiotherapy are very recommended. Although there was postoperative recurrence in our patient, radiotherapy was shown to be effective and affecting patient quality of life. However, there are only a few reports regarding successful radiotherapy procedure for YST have been reported so far.

Apoptotic death was reported to be an essential factor for tumor sensitivity to radiotherapy or chemotherapy. p53 is suspected to functionate as a control checkpoint for responding if there is any DNA damage and plays role in the apoptosis induction [21]. Cells with functionless p53, induced by the loss of p53 gene mutation, are unable to recognize DNA damage and initiate apoptosis. Investigation of rat YST's, including wild-type and radiation-resistant cell lines, demonstrated that p53 gene status influenced differences in apoptosis and radiosensitivity of both cell lines [22]. VP16 also has been reported to increase radiation-induced apoptosis in radiation-resistant cell lines [23]. In addition, CDDP combined with early radiation has been reported to have an additive effect in both cell lines [24]. Resistance also may have been acquired after repeated chemotherapy. We also concluded that the chemotherapy may have either increased tumor radiosensitivity or killed all radioresistant tumor cells. Due to inconsistent reports on actual clinical cases of YST, the recommended radiation dose and treatment plan are also yet to be determined. However, considering the tolerable radiation dose to surrounding organs and areas, the patient's general condition, and

the degree of tumor shrinkage during radiotherapy, the radiation dose used for this patient may be given appropriately.

Our case is unique due to the patient had an extensive intra-abdominal spread of the YST that she could not survive even after having tumor reduction by surgery, chemotherapy, and radiotherapy. Although radiotherapy helped her relieving her symptoms, it could not improve the survival chance. There are case reports in which researchers reported that radiotherapy positively affects the prognosis of the disease. Sakaguchi et al. [25] reported a similar case of postoperative recurrent YST in which radiotherapy proved to be a valuable treatment option and saved the patient.

We conclude from our case report that radiotherapy can be a valuable treatment options in patients with YSTs. However, it does not ensure the survival of the patient as the prognosis depends upon various factors like the recurrence of the tumor, metastasis, extragonadal involvement, and what kind of treatment has been done at the early stages of the disease. Further studies on a large number will be necessary to validate the utility of radiotherapy for YST cases.

Acknowledgements

Big thanks to the patient and her family, the friends who helped in the process and gave a huge contribution to this study, and to Cancer Centre of Santosa Hospital Bandung Kopo.

Statement of Ethics

Written informed consent was obtained from the patient and her family for publication of this case report and any accompanying image. This study has been approved by Research Ethic Committee of Padjadjaran University (KEP-*Komite Etik Penelitian Universitas Padjadjaran*) and gained ethical clearance by number 901/UN6.KEP/EC/2020.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This article does not receive any funding from any institution.

Author Contributions

Marhendra Satria Utama as corresponding author has contributed to this article by concepting the design, interpretation of the case, and as final decision maker for the final version of this article. Andi Kurniadi as coauthor has contributed to this article by concepting the design and interpretation of the case. A.A. Citra Yunda Prahastiwi as coauthor has contributed to this article by concepting the design and interpretation data of the case. Antony A. Adibrata as coauthor has contributed to this article by drafting the word and revising content of the article.

References

1 Kurman RJ, Norris HJ. Malignant germ cell tumors of the ovary. Hum Pathol. 1977 Sep;8(5):551–64.
2 Gershenson DM, Morris M, Cangir A, Kavanagh JJ, Stringer CA, Edwards CL, et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin. J Clin Oncol. 1990 Apr;8(4):715–20.
3 Nawa A, Obata N, Kikkawa F, Kawai M, Nagasaka T, Goto S, et al. Prognostic factors of patients with yolk sac tumors of the ovary. Am J Obstet Gynecol. 2001;184(6):1182–8.
4 Guo YL, Zhang YL, Zhu JQ. Primary yolk sac tumor of the retroperitoneum: a case report and review of the literature. Oncol Lett. 2014 Aug;8(2):556–60.
5 DiPerna CA, Bowdish ME, Weaver FA, Bremner RM, Jabbour N, Skinner D, et al. Concomitant vascular procedures for malignancies with vascular invasion. Arch Surg. 2002 Aug;137(8):901–7.
6 Cicin I, Saip P, Guney N, Eralp Y, Ayan I, Kebudi R, et al. Yolk sac tumours of the ovary: evaluation of clinicopathological features and prognostic factors. Eur J Obstet Gynecol Reprod Biol. 2009 Oct;146(2):210–4.
7 Peccatori F, Bonazzi C, Chiari S, Landoni F, Colombo N, Mangioni C. Surgical management of malignant ovarian germ-cell tumors: 10 years' experience of 129 patients. Obstet Gynecol. 1995 Sep;86(3):367–72.
8 Ayhan A, Bildirici I, Günalp S, Yuce K. Pure dysgerminoma of the ovary: a review of 45 well staged cases. Eur J Gynaecol Oncol. 2000;21(1):98–101.
9 Zanagnolo V, Sartori E, Galleri G, Pasinetti B, Bianchi U. Clinical review of 55 cases of malignant ovarian germ cell tumors. Eur J Gynaecol Oncol. 2004;25(3):315–20.
10 Dede M, Pabuccu R, Yagci G, Yenen MC, Goktolga U, Gunhan O. Extragonadal yolk sac tumor in pelvic localization. A case report and literature review. Gynecol Oncol. 2004;92(3):989.
11 Alkatan HM, Al-Kofide A, Al-Hussain H. Yolk sac tumor: histopathologic report of 2 cases. Can J Ophthalmol. 2008 Feb;43(1):125–6.
12 Bokemeyer C, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, et al. Extragonadal seminoma: an international multicenter analysis of prognostic factors and long term treatment outcome. Cancer. 2001 Apr;91(7):1394–401.
13 Bailey J, Church D. Management of germ cell tumours of the ovary. Rev Gynaecol Pract. 2005;5(4):201–6.
14 Sell A, Sogaard H, Norgaard-Pedersen B. Serum alpha-fetoprotein as a marker for the effect of post-operative radiation therapy and/or chemotherapy in eight cases of ovarian endodermal sinus tumour. Int J Cancer. 1976;18(5):574–80.
15 Mitchell PL, Al-Nasiri N, A'Hern R, Fisher C, Horwich A, Pinkerton CR, et al. Treatment of nondysgerminomatous ovarian germ cell tumors: an analysis of 69 cases. Cancer. 1999;85:2232–44.
16 Talerman A, Haije WG, Baggerman L. Serum alphafetoprotein (AFP) in patients with germ cell tumors of the gonads and extragonadal sites: correlation between endodermal sinus (yolk sac) tumor and raised serum AFP. Cancer. 1980 Jul;46(2):380–5.
17 Tozzi R, Schneider A. Laparoscopic treatment of early ovarian cancer. Curr Opin Obstet Gynecol. 2005 Aug;17(4):354–8.
18 De Corti F, Sarnacki S, Patte C, Mosseri V, Baranzelli MC, Martelli H, et al. Prognosis of malignant sacrococcygeal germ cell tumours according to their natural history and surgical management. Surg Oncol. 2012;21(2):e31–7.
19 National Guideline Clearinghouse. Ovarian germ cell tumours. Available from: https://www.guideline.gov/content.aspx?id=47845. Accessed 2016 May 3.
20 de La Motte Rouge T, Pautier P, Duvillard P, Rey A, Morice P, Haie-Meder C, et al. Survival and reproductive function of 52 women treated with surgery and bleomycin, etoposide, cisplatin (BEP) chemotherapy for ovarian yolk sac tumor. Ann Oncol. 2008 Aug;19(8):1435–41.
21 Levine AJ, Momand J, Finlay CA. The p53 tumour suppressor gene. Nature. 1991 Jun;351(6326):453–6.
22 Maebayashi K, Mitsuhashi N, Takahashi T, Sakurai H, Niibe H. p53 mutation decreased radiosensitivity in rat yolk sac tumor cell lines. Int J Radiat Oncol Biol Phys. 1999 Jun;44(3):677–82.
23 Takahashi T, Mitsuhashi N, Akimoto T, Matsumoto H, Ishikawa H, Saito Y, et al. Interaction of radiation and etoposide on two cell lines with different radiosensitivities in vitro. Anticancer Res. 2003;23(4):3459–64.
24 Nakamoto S, Mitsuhashi N, Takahashi T, Sakurai H, Niibe H. An interaction of cisplatin and radiation in two rat yolk sac tumour cell lines with different radiosensitivities in vitro. Int J Radiat Biol. 1996;70(6):747–53.
25 Sakaguchi M, Maebayashi T, Aizawa T, Ishibashi N, Fukushima S, Saito T. Successful radiotherapy in postoperative recurrence of a primary mediastinal yolk sac tumor: a case report. Thorac Cancer. 2016;7(3):358–62.