How to Cite:
Alnagmy, A., Zaghloul, M. S., Mahmoud, M., Aboelkasem, H., Mokhtar, M. H., & Awad, A. (2022). Dosimetric comparison between intensity modulated radiotherapy and three-dimensional conformal radiotherapy in adjuvant setting after radical cystectomy in high-risk urothelial bladder cancer . *International Journal of Health Sciences*, *6*(S6), 7366–7375. https://doi.org/10.53730/ijhs.v6nS6.11819

Dosimetric comparison between intensity modulated radiotherapy and three-dimensional conformal radiotherapy in adjuvant setting after radical cystectomy in high-risk urothelial bladder cancer

Ahmed Alnagmy
Radiation Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt
Corresponding author email: ahmed.alnagmy86@cu.edu.eg
https://orcid.org/0000-0001-5092-8067

Mohamed S. Zaghloul
Radiation Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Mohamed Mahmoud
Radiation Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Hatem Aboelkasem
Surgical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Maha H. Mokhtar
Physics Unit, Radiation Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Ahmed Awad
Radiation Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

***Abstract*---**Objective: To compare the 4-field 3D conformal radiotherapy technique (3DCRT) to the intensity-modulated radiotherapy (IMRT) 9-field technique for adjuvant radiotherapy post radical cystectomy in high-risk urothelial bladder cancer cases. Patients and Methods: A dosimetric analysis of 11 urothelial bladder cancer patients who underwent radical cystectomy was performed. These patients were presented to the radiotherapy department,

Manuscript submitted: 9 April 2022, Manuscript revised: 18 June 2022, Accepted for publication: 27 July 2022

National Cancer Institute, Cairo, between 2018 and 2020 with adjuvant radiotherapy using the IMRT technique. Two plans were designed for each patient, one using 9-field IMRT and the second using 4-field 3DCRT. The two techniques were compared, including the PTV, bowel bag, rectum, neobladder, and pelvic bone marrow. Results: Comparing different DVHs, the planning target volume (PTV) was adequately covered in both plans, while the 9-field IMRT technique delivered significantly lower doses to OARs (bowel, rectum, and pelvic bone marrow). Conclusion: The IMRT technique incredibly spared the OARs more than that obtained by the 3DCRT technique, while both techniques covered the PTV adequately. The IMRT technique, through sparing OARs, was expected to decrease early and late radiation side effects.

Keywords---Urothelial cancer, postoperative radiotherapy, Dosimetric study, IMRT, 3DCRT.

Introduction

Radical cystectomy with bilateral pelvic lymph nodes dissection (PLND) is the current gold-standard treatment for muscle-invasive bladder cancer (MIBC) (El Sebaie, 1978, Stenzl et al., 2005). The loco-regional recurrence (LRR) rates varied in SWOG 8710 randomized trial (neoadjuvant chemotherapy vs. cystectomy alone in patients with locally advanced bladder cancer (≥ pT3, pN+ or positive R1 surgical margins) as 32%, 29%, and 68% respectively (Herr et al., 2004). The impact of the LRR on survival is highly significant as patient survival after loco-regional recurrence does not usually exceed 4 to 8 months (Cagiannos & Morash, 2009). Loco-regional control was directly correlated to overall survival (OS) benefit (Skinner et al., 2007).

However early studies showed that adjuvant radiotherapy (RT) for high-risk bladder cancer reduced LRR and improved disease-free survival (DFS) and OS when compared to cystectomy alone (Zaghloul et al., 1986 & 1992). A decreased interest in adjuvant RT was noticed decades ago due to the high gastrointestinal (GI) toxicity reported by Reisinger et al., 1992. It is worth noting that the older RT techniques using two-dimensional plans in the 1970s-1980s were the primary factor in such high GI complications. These historical studies of adjuvant RT have used 2D RT entailing 3-4 fields technique (opposed AP/PA beams and opposed lateral beams or anterior and 2 wedged lateral fields) (Zaghloul, 2010). Many investigators started to believe in the efficacy and tolerability of adjuvant RT with the continuous advancement in surgical and radiotherapy techniques (Zaghloul et al., 1992 & 2018). However, the doses received by the organs at risk, such as the rectum, femoral heads, and the small intestine, resulted in severe acute and late toxicities. These side effects limited the use of adjuvant RT, particularly in western countries (Sargos et al., 2016).

Adjuvant RT using the 3DCRT technique was well tolerated in the Egyptian trial where late grade 3+ GI toxicity for the adjuvant chemo-radiotherapy when using modern 3DCRT down to 7% (Zaghloul et al., 2018). Only one trial in the English literature has examined several RT techniques to determine the effect of each modality on the intestinal and rectal dose. The study proved that IMRT and pencil beam scanned proton RT had dosimetric advantages against 3DCRT in improving rectal and bowel dose with no significant differences compared to proton and IMRT techniques (Baumann et al., 2015). The recent multicentric phase 2 trial reported acute grade 2 gastrointestinal (GI) toxicity in 42 patients (61%), while 6% experienced acute grade 3 GI toxicity (4 patients). However, grade 5 diarrhea and vomiting were reported in only one patient due to the development of intestinal obstruction at 1-month post-therapy. The patients received 50 Gy/25 fx/5 weeks using IMRT to the pelvic lymph nodes ± cystectomy bed. Simultaneous integrated boost (SIB) of up to 70 Gy was delivered to suspicious lymph nodes detected in 18F-FDG-PET-CT. The study suggested that adjuvant RT resulted in good LC and acceptable toxicity (Fonteyne et al., 2021).

Patients and methods

Eleven patients with high-risk urothelial bladder cancer (pT3+/pN+/high grade) presented to the radiotherapy department at National Cancer Institute, Cairo, between 2018 and 2020 and received postoperative radiotherapy using the IMRT technique. Eight patients had ileal conduit diversions, and three had an orthotopic neobladder. All patients were scanned using a CT simulator in a supine position with immobilization by knee and ankle rest support after rectal preparation using a laxative enema. CT scan slices with a thickness of 2.5 mm were obtained from the top of L1 to 2 cm below the ischial tuberosities. The CT images were automatically transferred to an Eclipse planning workstation, where the CTV and relevant organs-at-risk (OARs) were delineated.

Treatment Plan

- Targets:
  - Clinical Target volume (CTV) includes the external and internal iliac, pre-sacral, obturator lymph nodes, and the bladder bed.
  - Planning Target Volume (PTV) is created by adding 7 mm isocentrically to CTV.
  - Contouring was done according to International Consensus Contouring Guidelines for Adjuvant Radiation after Radical Cystectomy for Bladder cancer (Baumann et al., 2016, Verghote et al., 2022).
- Organs at Risk:
  Intestine, rectum, bone marrow, femoral heads, neobladder, or stoma if present.

Table 1
Plan Acceptance Criteria

Structure	Dose constraint	Reference
PTV	• D95% is 100% of the prescribed dose, acceptable deviation of 95% • D2% ≤ 107 % of the planned absorbed dose	ICRU Report 83 (Gregoire & Mackie, 2011).

Table 1
Plan Acceptance Criteria

Structure	Dose constraint	Reference
Bowel bag	• V45Gy less than 195cc	QUANTEC (Marks et al., 2010).
	• Acceptable deviation up to 250cc	Target Volume Delineation for Conformal and Intensity Modulated Radiation Therapy (Lee et al., 2015).
Rectum	• V30Gy less than 95% • V40Gy less than 75% • V50Gy less than 50%	EMBRACE II (Pötter et al., 2018). QUANTEC (Marks et al., 2010).
Pelvic bone marrow	• Mean dose less than 28Gy • V10Gy less than 90% • V20Gy less than 75%	Target Volume Delineation for Conformal and Intensity Modulated Radiation Therapy (Lee et al., 2015).

Treatment Planning

Two plans were generated for each patient, one using the 9-field IMRT and the other using 4-field 3DCRT. The two techniques were compared using dose volume histogram (DVH) analysis of the PTV, bowel bag, rectum, and pelvic bone marrow. Both treatment plans were performed using the Eclipse treatment planning system (TPS) using 5 mm leaf width and 6 MV photon energy.

Statistical analysis

A simple t-test was used to compare mean values ± 95% confidence interval for different DVH parameters between the two treatment techniques, with a p-value ≤ 0.05 considered statistically significant.

Results

Effect of treatment technique on PTV coverage

ICRU 83 recommends reporting D95% and D2%. D95% is the minimum absorbed dose that covers 95% of the volume of the PTV. D2% is the near maximum dose as a replacement for the “maximum absorbed dose (Gregoire & Mackie, 2011). The D95% of the PTV received at least 95% of the prescribed dose in both plans with no significant difference (p= 0.9). D2% was less than 107% of the prescribed dose in both plans with no significant difference (p=0.3) (Table 2).

Table 2
Comparison of PTV parameters between both techniques

Parameter	IMRT N= 11	3DCRT N= 11	P value
D95%	48.41±0.62	48.51±0.43	0.9104
D2%	52.46±1.17	52.53±0.24	0.3048
Conformity index	1.1±0.04	1.7±0.09	<0.0001
Homogeneity index	0.1±0.03	0.09±0.01	0.1229

Effect of treatment technique on bowel toxicity

The V30, V40, and V45 of the bowel were significantly lower in the IMRT plan than 3DCRT (P=0.006, P= <0.0001, P= <0.0001, respectively). These results denote that the IMRT plan effectively decreased the volume of irradiated bowel exposed to clinically significant doses; e.g., V45 was 194.37±33.19 versus 394.78±93.44 in IMRT versus 3DCRT, respectively (Table 3) (Figure 1).

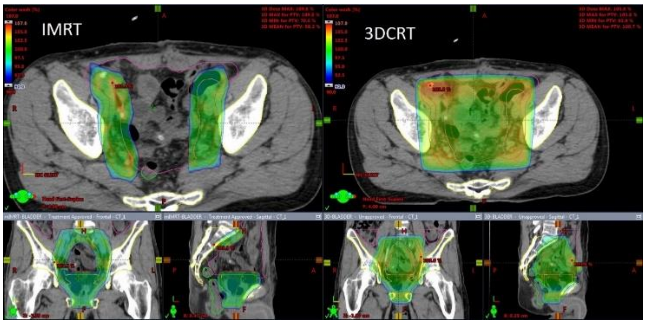

Figure 1. Bowel sparing using the IMRT technique

Effect of treatment technique on rectal toxicity

The V30, V40, and V50 of the rectum were significantly lower in the IMRT plan compared to the 3DCRT plan (P=0.0004, P= 0.0013, P=0.0008, respectively) (Table 3) (Figure 2).

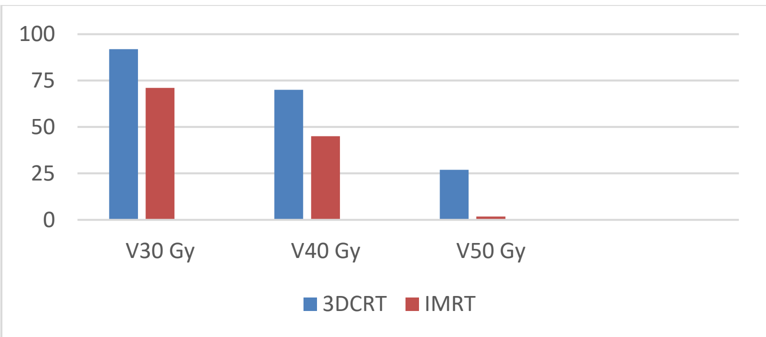

Figure 2. Chart showing dose to the rectum in both techniques

Effect of treatment technique on pelvic bone marrow toxicity

The IMRT plan has been shown to decrease all bone marrow-related parameters effectively, resulting in good bone marrow sparing, e.g., the mean dose was 27.88±0.91 in the IMRT plan versus 36.95±1.2 in the 3DCRT plan (p=<0.0001) (Table 3).

Table 3
Comparison of doses to organs at risk between both techniques

Parameter	IMRT N= 11	3DCRT N= 11	P value
Bowel			
V30 Gy	465.06±86.65	636.34±109.2	0.0006
V40 Gy	274.49±53.87	449.75±87.73	<0.0001
V45 Gy	194.37±33.19	394.78±93.44	<0.0001
Rectum			
V30	70.61±13.3	92.05±8.7	0.0004
V40	44.59±12.22	70.43±13.86	0.0013
V50	7.91±6.77	27.04±15.13	0.0008
Pelvic bone marrow			
Mean	27.88±0.91	36.95±1.2	<0.0001
V10	90.7±2.14	95.87±1.77	<0.0001
V20	65.63±4.7	91.55±2.4	<0.0001
V40	23.82±2,44	42.45±4.84	<0.0001
Neobladder			
Mean	43.5±4.24	46.9±1.13	0.6667

Discussion

The present results showed no significant difference in PTV coverage with adequate coverage in both techniques, matching the results of Baumann et al., 2015 comparing 3DCRT, IMRT, and pencil beam proton radiotherapy with no significant difference regarding PTV coverage. Reisinger et al., 1992 reported a 37% incidence of late bowel toxicity in a series of patients who received both pre- and postoperative RT with an equivalent total dose (50 Gy), reaching 22.5% grade 4 and 7.5% grade 5. The high rate of toxicity they reported with adjuvant RT was likely attributable to a combination of RT-specific dose levels received by the large volume of OAR, as well as the high adverse event rates experienced with cystectomy. It is worth noting that these radiation-specific factors include the use of outdated 2-D RT techniques, vast RT treatment fields, and the use of AP/PA field arrangements, which would increase the small intestinal dose in comparison to other field arrangements. There are scarce USA Adjuvant RT studies, mainly using 2 D RT and older surgical techniques. These studies reported high toxicities leading to a decreased interest in adjuvant RT, despite the relatively modest added toxicity of adjuvant RT (Baumann et al., 2017).

Furthermore, there is evidence that intensity-modulated radiotherapy (IMRT) reduces the risk of acute and late morbidity in different pelvic tumor management (Gandhi et al., 2013; Mundt et al., 2003). IMRT is instrumental in reducing the incidence of bowel morbidity and may also reduce urinary morbidity (Pötter et al., 2018). According to Marks et al., 2010, the volume of bowel that received 45 Gy or more (V45 Gy) is recommended to be less than 195cc of the entire potential space within the peritoneal cavity when using concurrent chemotherapy to limit the grade ≥ 3 acute toxicity below 10%. In our study, the IMRT plan decreased the volume of bowel exposed to high dose by nearly 50% (V45 was 194.37±33.19 versus 394.78±93.44 in IMRT and 3DCRT, respectively). This reduction is assumed to impact early and late GIT toxicity significantly.

Moreover, Forrest et al., 2012 found a significant reduction in the dose to the rectum at the V50, V45, V40, and V30 levels with a difference of 84% in the rectum for V50Gy in most patients without compromising target coverage when comparing IMRT with 3DCRT for definitive management of cervical cancer. Yang et al., 2012 reported a 40% reduction in rectal volume receiving 40Gy in !3 dosimetric studies meta-analysis of 13 dosimetric studies comparing 3DCRT and IMRT treatment plans in gynecologic malignancy. This result is consistent with the findings of Chan et al., 2006 who found that using the eight fields of IMRT reduced rectal volume by about 22%. The present study showed that IMRT significantly decreased rectal V30 Gy by 21%, V40Gy by almost 26%, and V50Gy by 19% in gynecologic malignancy. This finding suggests the same improvement in rectal toxicity with IMRT in bladder cancer.

Rose et al., 2011 reported that patients with V10 ≥ 95% were more likely to experience grade 3 leukopenia than were patients with V20 > 76%. According to RTOG 0418 phase II clinical trial, among cervical cancer patients with a V40 >37%, 75% had grade 2 or higher hematological toxicity compared with 40% of patients with a V40 less than or equal to 37% (P =0.025). In addition, a median bone marrow dose of >34.2 Gy also had higher rates of grade 2 hematological toxicity than did those with a dose of <34.2 Gy (74% vs. 43%, P=0.049) in cervical carcinoma (Klopp et al., 2013). Our study showed good bone marrow sparing using IMRT, which significantly decreased pelvic bone marrow mean dose by 9% (p= <0.0001). V10 also decreased by 5% (p= <0.0001), V20 by 26% (p= <0.0001) and V40 by nearly 19% (p= <0.0001). This finding points to the feasibility of bone marrow sparing using IMRT, which suggests a positive impact on hematological toxicity.

Conclusions

From the present study, we concluded that the IMRT technique spared more efficiently OARs (bowel, rectum, and pelvic bone marrow) than the 3DCRT technique. In contrast, both techniques adequately covered the PTV with nearly no difference in this coverage. So, the IMRT technique should be used whenever adjuvant treatment after radical cystectomy in urothelial bladder cancer patients is needed.

References

Baumann, B. C., Noa, K., Wileyto, E. P., Bekelman, J. E., Deville, C., Vapiwala, N., Kirk, M., Both, S., Dolney, D., Kassaee, A., & Christodouleas, J. P. (2015). Adjuvant radiation therapy for bladder cancer: A dosimetric comparison of techniques. Medical Dosimetry, 40(4), 372–377. https://doi.org/10.1016/j.meddos.2015.06.001

Cagiannos, I., & Morash, C. (2009). Surveillance strategies after definitive therapy of invasive bladder cancer. Journal of the Canadian Urological Association, 3(6 SUPPL. 4), 237–242. https://doi.org/10.5489/cuaj.1205

Chan, P., Yeo, I., Perkins, G., Fyles, A., & Milosevic, M. (2006). Dosimetric comparison of intensity-modulated, conformal, and four-field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study. Radiation Oncology, 1(1), 13. https://doi.org/10.1186/1748-717X-1-13

Fonteyne, V., Dirix, P., Van Praet, C., Berghen, C., Albersen, M., Junius, S., Liefhooghe, N., Noé, L., De Meerleer, G., Ost, P., Villeirs, G., Verbeke, S., De Maeseneer, D., Rammant, E., Verghote, F., Elhaseen, E., De Man, K., & Decaestecker, K. (2021). Adjuvant Radiotherapy After Radical Cystectomy for Patients with High-risk Muscle-invasive Bladder Cancer: Results of a Multicentric Phase II Trial. European Urology Focus, xxxx. https://doi.org/10.1016/j.euf.2021.11.004

Forrest, J., Presutti, J., Davidson, M., Hamilton, P., Kiss, A., & Thomas, G. (2012). A Dosimetric Planning Study Comparing Intensity-modulated Radiotherapy with Four-field Conformal Pelvic Radiotherapy for the Definitive Treatment of Cervical Carcinoma. Clinical Oncology, 24(4), e63–e70. https://doi.org/10.1016/j.clon.2011.06.008

Gandhi, A. K., Sharma, D. N., Rath, G. K., Julka, P. K., Subramani, V., Sharma, S., Manigandan, D., Laviraj, M. A., Kumar, S., & Thulkar, S. (2013). Early Clinical Outcomes and Toxicity of Intensity Modulated Versus Conventional Pelvic Radiation Therapy for Locally Advanced Cervix Carcinoma: A Prospective Randomized Study. International Journal of Radiation Oncology*Biology*Physics, 87(3), 542–548. https://doi.org/10.1016/j.ijrobp.2013.06.2059

Gregoire, V., & Mackie, T. R. (2011). Dose prescription , reporting and recording in intensity-modulated radiation therapy : a digest of the ICRU Report 83. 3, 367–373.

Herr, H. W., Faulkner, J. R., Grossman, H. B., Natale, R. B., deVere White, R., Sarosdy, M. F., & Crawford, E. D. (2004). No Title. Journal of Clinical Oncology, 22(14), 2781–2789. https://doi.org/10.1200/JCO.2004.11.024

Klopp, A. H., Moughan, J., Portelance, L., Miller, B. E., Salehpour, M. R., Hildebrandt, E., Nuanjing, J., D'Souza, D., Souhami, L., Small, W., Gaur, R., & Jhingran, A. (2013). Hematologic Toxicity in RTOG 0418: A Phase 2 Study of Postoperative IMRT for Gynecologic Cancer. International Journal of Radiation Oncology*Biology*Physics, 86(1), 83–90. https://doi.org/10.1016/j.ijrobp.2013.01.017

Lee, N. Y., Riaz, N., & Lu, J. J. (Eds.). (2015). Target Volume Delineation for Conformal and Intensity-Modulated Radiation Therapy. Springer International Publishing. https://doi.org/10.1007/978-3-319-05726-2

Marks, L. B., Yorke, E. D., Jackson, A., Ten Haken, R. K., Constine, L. S., Eisbruch, A., Bentzen, S. M., Nam, J., & Deasy, J. O. (2010). Use of Normal Tissue Complication Probability Models in the Clinic. International Journal of Radiation Oncology Biology Physics, 76(3 SUPPL.). https://doi.org/10.1016/j.ijrobp.2009.07.1754

Mundt, A. J., Mell, L. K., & Roeske, J. C. (2003). Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. International Journal of Radiation Oncology*Biology*Physics, 56(5), 1354–1360. https://doi.org/10.1016/S0360-3016(03)00325-0

Pötter, R., Tanderup, K., Kirisits, C., de Leeuw, A., Kirchheiner, K., Nout, R., Tan, L. T., Haie-Meder, C., Mahantshetty, U., Segedin, B., Hoskin, P., Bruheim, K., Rai, B., Huang, F., Van Limbergen, E., Schmid, M., Nesvacil, N., Sturdza, A., Fokdal, L., … Jürgenliemk-Schulz, I. (2018). The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clinical and Translational Radiation Oncology, 9, 48–60. https://doi.org/10.1016/j.ctro.2018.01.001

Reisinger, S. A., Mohiuddin, M., & Mulholland, S. G. G. (1992). Combined pre- and postoperative adjuvant radiation therapy for bladder cancer-A ten year experience. International Journal of Radiation Oncology, Biology, Physics, 24(3), 463–468. https://doi.org/10.1016/0360-3016(92)91060-Z

Rose, B. S., Aydogan, B., Liang, Y., Yeginer, M., Hasselle, M. D., Dandekar, V., Bafana, R., Yashar, C. M., Mundt, A. J., Roeske, J. C., & Mell, L. K. (2011). Normal Tissue Complication Probability Modeling of Acute Hematologic Toxicity in Cervical Cancer Patients Treated With Chemoradiotherapy. International Journal of Radiation Oncology*Biology*Physics, 79(3), 800–807. https://doi.org/10.1016/j.ijrobp.2009.11.010

Skinner, E. C., Stein, J. P., & Skinner, D. G. (2007). Surgical benchmarks for the treatment of invasive bladder cancer. Urologic Oncology: Seminars and Original Investigations, 25(1), 66–71. https://doi.org/10.1016/j.urolonc.2006.05.010

Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). The COVID-19 pandemic. International Journal of Health Sciences, 5(2), vi-ix. https://doi.org/10.53730/ijhs.v5n2.2937

Thaib, P. K. P., & Rahaju, A. S. (2022). Clinicopathological profile of clear cell renal cell carcinoma. International Journal of Health & Medical Sciences, 5(1), 91-100. https://doi.org/10.21744/ijhms.v5n1.1846

Verghote, F., Sargos, P., Christodouleas, J. P., Murthy, V., Baumann, B. C., Dirix, P., Berghen, C., Paelinck, L., Vercauteren, T., & Fonteyne, V. (2022). International Consensus Guidelines for Adjuvant Radiation Therapy for Bladder Cancer After Radical Cystectomy: Update From an IBIS Workgroup. Practical Radiation Oncology. https://doi.org/10.1016/j.prro.2022.05.014

Yang, B., Zhu, L., Cheng, H., Li, Q., Zhang, Y., & Zhao, Y. (2012). Dosimetric comparison of intensity modulated radiotherapy and three-dimensional conformal radiotherapy in patients with gynecologic malignancies: a systematic review and meta-analysis. Radiation Oncology, 7(1), 197. https://doi.org/10.1186/1748-717X-7-197

Zaghloul, M. S. (2010). Adjuvant and neoadjuvant radiotherapy for bladder cancer: Revisited. Future Oncology, 6(7), 1177–1191. https://doi.org/10.2217/fon.10.82

Zaghloul, M. S., Awwad, H. K., Akoush, H. H., Omar, S., Soliman, O., & Attar, E. L. (1992). Postoperative Radiotherapy Of Carcinoma In Bilharzial Bladder: Improved Disease Free Survival Through Improving Local Control. In Radiation Oncology Bid. Phys (Vol. 23).

Zaghloul, M. S., Christodouleas, J. P., Smith, A., Abdallah, A., William, H., Khaled, H. M., Hwang, W. T., & Baumann, B. C. (2018). Adjuvant sandwich chemotherapy plus radiotherapy vs adjuvant chemotherapy alone for locally advanced bladder cancer after radical cystectomy a randomized phase 2 trial. JAMA Surgery, 153(1). https://doi.org/10.1001/jamasurg.2017.4591