

External Beam Radiotherapy for Carcinoma of the Extrahepatic Biliary System

Ha Chung Chun M.D. and Myung Za Lee M.D.

Department of Radiation Oncology, Hanyang University Medical School

= Abstract =

Purpose : To evaluate the effectiveness and tolerance of patients of external beam radiotherapy for carcinoma of the extrahepatic biliary system (EHBS) including gall bladder (GB) and extrahepatic bile ducts (EHBD) and to define the role of radiotherapy for these tumors.

Methods and Materials : We retrospectively analyzed the records of 43 patients with carcinoma of the EHBS treated with external beam radiotherapy at our institution between April, 1986 and July, 1994. Twenty three patients had GB cancers and remaining 20 patients did EHBD cancers. Of those 23 GB cancers, 2 had Stage II, 12 did Stage III and 9 did Stage IV disease, respectively. Male to female ratio was 11 to 12. Fifteen patients underwent radical surgery with curative intent and 8 patients did biopsy and bypass surgery alone. All of the patients except for 3 patients were treated with 4500 cGy or higher doses postoperatively. Follow up periods ranged from 11 to 82 months. Of those 20 EHBD cancers, one had Stage I, 2 did Stage II, 10 did Stage III and 7 did Stage IV disease, respectively. Male to female ratio was 16 to 4. Sixteen patients underwent Whipple's procedure or resection and drainage with curative aim and remaining 4 patients did bypass surgery alone. Postoperatively 16 patients were irradiated with 4500 cGy or higher doses and 4 patients with 3180 to 4140 cGy. Follow up periods ranged from 8 to 34 months.

Results : Overall median survival time of patients with GB cancer was 11 months. Median survival time for patients with Stage III and IV disease were 14 months and 5 months, respectively. Corresponding two year survival rates were 36%(4/11) and 13%(1/8), respectively. Those who underwent surgery with curative intent showed significantly better survival at 12 months than those who underwent bypass surgery alone(67% vs 13%). None of the patients died of treatment related complications. Median survival time for entire group of 20 EHBD patients was 10 months. Median survivals of 10 Stage III and 7 Stage IV disease were 10 and 8 months, respectively. Two patients who underwent Whipple's procedure had 11 and 14 month survival and those treated with resection and drainage showed median survival of 10 month.

Conclusion : Postoperative external beam radiotherapy for carcinoma of the extrahepatic biliary system is well tolerated and might improve survival of patients, especially those with resectable lesions with microscopic or gross residual disease after surgery.

Key Words: Gall bladder cancer, Bile duct cancer, Radiotherapy

INTRODUCTION

Primary malignancies of the gall bladder (GB) or extrahepatic bile ducts (EHBD) are uncommon, but highly lethal. Most series report overall 5-year survival less than 10% and approximately 20–30% of tumors are resectable at presentation¹⁻⁷. The main routes of spread are by direct invasion to adjacent structures and early metastases to regional lymph nodes in 40–50% of patients^{7, 8}. Retroperitoneal nodal involvement occurs in 15–26% of patients^{8, 9}. Peritoneal spread occurs in 20% of patients with GB cancers⁸ and in 9% of patients with EHBD cancers⁹. The liver is also involved at an early stage because of direct extension or metastases⁷. Deaths from these cancers are usually results of local regional disease, instead of distant metastases.

In the past, these lesions have been considered resistant to radiation. Early experience with external radiation therapy demonstrated good palliation with occasional long term survival and suggested of better results with higher dose^{7, 10-12}. To attain higher doses without exceeding normal tissue tolerance, several groups have more recently used intraoperative techniques¹³⁻¹⁵ or brachytherapy¹⁴⁻²². Results to date appear promising, but the numbers of patients are small and follow up periods are short.

We retrospectively analyzed the record of 43 patients with carcinoma of the GB and EHBD treated with external beam radiotherapy at our Department to evaluate the effectiveness and tolerance of radiotherapy and to define the role of radiotherapy for these tumors.

METHODS AND MATERIALS

We retrospectively analyzed the records of 43 patients with carcinoma of the extrahepatic biliary system (EHBS) treated with external beam radiotherapy at our institution between April, 1986 and July, 1994. Twenty three patients had gall bladder cancers and remaining 20 patients did extrahepatic bile duct cancers. All of the patients underwent surgical procedures to obtain histological diagnosis and were retrospectively restaged according to American Joint Committee on Cancer (AJCC) staging system.

Prior to surgical procedures, patients were evaluated with percutaneous transhepatic cholangiography (PTHC), endoscopic retrograde cholangiopancreatography (ERCP), Computed Tomography (CT) or sonography of the upper abdomen or sonography.

Of those 23 patients with GB cancers, 2 had Stage II disease, 12 did Stage III disease, and 9

Table 1. Distribution of Patients according to AJCC Staging System

	Gall Bladder	Extrahepatic Bile Duct
Stage I	0	1
Stage II	2	2
Stage III	12	10
Stage IV	9	7
Total	23	20

Table 2. Presenting Symptoms at Initial Diagnosis

Gall Bladder	Extrahepatic Bile Duct
epigastric pain or discomfort (21)	Jaundice (18)
jaundice (4)	Abdominal pain (4)
abdominal mass (3)	fever (3)
indigestion (2)	pruritus (2)
fever (1)	nausea (1)
pruritus (1)	fatigue (1)
	abdominal mass (1)

Table 3. Distribution of Patients according to Type of Surgery

	Gall Bladder	Extrahepatic Bile Duct
Radical	15	Whipple 2
Bypass	8	Resection and Drainage 14
		Bypass 4
Total	23	20

did Stage IV disease, respectively (Table 1). Male to female ratio of GB cancers (11 to 12) was definitely lower than that of EHBD cancers (16 to 4). Presenting symptoms at initial diagnosis were epigastric pain or discomfort, jaundice, abdominal mass, indigestion, fever and pruritus in decreasing order as shown in Table 2. Fifteen patients underwent radical surgery with curative intent and 8 patients did biopsy and bypass surgery alone (Table 3).

Of those 20 patients with EHBD cancers, one had Stage I disease, 2 did Stage II disease, 10 did Stage III disease and 7 did Stage IV disease, respectively. One patient with Stage I disease underwent cholecystectomy for cholelithiasis and turned out to have adenocarcinoma at the duct on pathological specimen. As mentioned above, male was predominant to female with ratio of 16 to 4. Presenting symptoms at initial diagnosis were jaundice, abdominal pain, fever, pruritus, nausea, fatigue and abdominal mass in decreasing order.

Sixteen patients underwent Whipple's procedure or resection and drainage with curative aim and remaining 4 patients did bypass surgery alone.

All of the patients were postoperatively treated with megavoltage external beam radiotherapy. They were irradiated with 6 or 10 MeV photons from Linear Accelerator. AP-PA portals were routinely employed. Treatment was given 5 times per week, once a day. Daily dose was either 180 or 200 cGy. Spinal cord was taken off at 4000 cGy with shrunk boost field.

Table 4 showed distribution of the patients according to total delivered dose.

Twenty of 23 patients with GB cancers and 16 of 20 patients with EHBD cancers received minimum of 4500 cGy. Although 7 patients received dose less

Table 4. Distribution of Patients according to dose

	Gall Bladder	Extrahepatic Bile Duct
<4500	3	4
4500	15	10
5000	4	4
>5000	1	2
Total	23	20

Table 5. Summary of Survival of Patients

Survival of Gall Bladder	
	Median
Overall	11 months
Stage III	14 months (36% at 2 year)
Stage IV	5 months (13% at 2 year)
Survival of Extrahepatic Bile Duct	
	Median
Overall	10 months
Stage III	10 months (30% at 1 year)
Stage IV	8 months (0% at 1 year)

than 4500 cGy, they were treated with minimum of 4000 cGy and considered to be treated with curative aim to get rid of microscopic residual disease.

Patients were followed by us or their referring physicians after irradiation.

Follow up periods ranged from 11 to 82 months for GB cancers and 8 to 34 months for EHBD cancers. Because of inadequate follow up information, we were not able to obtain exact local control or failure rate. However, patients were considered to die of local failure based on the fact that patients with these tumors usually die of infradiaphragmatic local failure⁷⁾. Actuarial survival was calculated from the first day of radiotherapy and statistical comparisons were done using Chi-square test.

RESULTS

1. Gall Bladder Cancer

Overall median survival time of patients with GB cancers was 11 months (Table 5). Two year survival rates for patients with Stage II, III and IV disease were 50% (1/2), 36% (4/11) and 13%(1/8), respectively.(Fig. 1) Median survival periods for patients

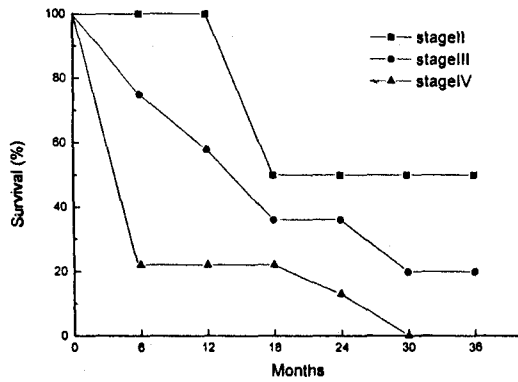


Fig. 1. Actuarial survival rates for GB cancers according to stage.

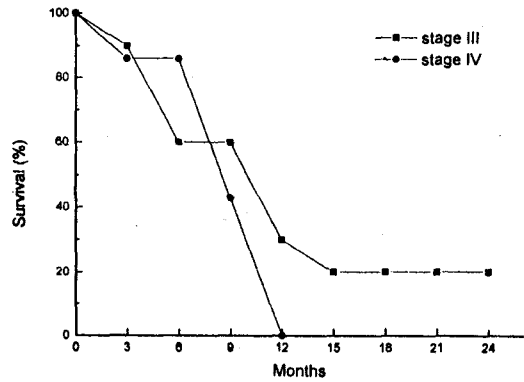


Fig. 3. Actuarial survival rates for extrahepatic bile duct cancers according to stage.

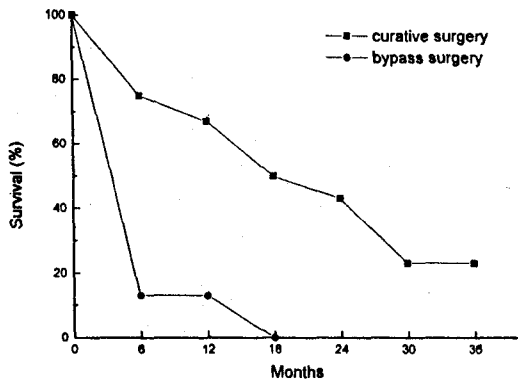


Fig. 2. Actuarial survival rates for GB cancers according to type of surgery.

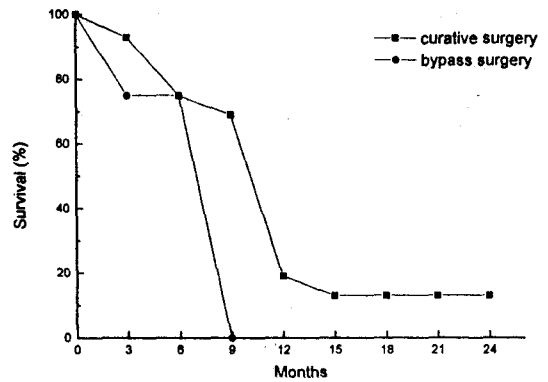


Fig. 4. Actuarial survival rates for extrahepatic bile duct cancers according to type of surgery.

with Stage III and IV disease were 14 months and 5 months. Those patients who were surgically treated with radical surgery showed significantly better survival than those treated with bypass surgery alone with p-value less than 0.5 (67% vs 13% at 12 month)(Fig. 2).

None of the patients died of treatment related complications.

2. Extrahepatic Bile Duct Cancer

Median survival time for entire group of 20 patients with EHBD cancers was 10 months as shown in Table 5. Median survival periods for patients with 10 Stage III disease and 7 Stage IV disease were

10 months and 8 months, respectively. One patient with Stage I disease died of recurrent disease at 13 month. Two patients with Stage II died of local recurrence at 9 and 10 months, respectively. Survival rates at 9 month for Stage III and IV patients were 60% and 43 %, respectively(Fig. 3).

Two patients who underwent Whipple's procedure died at 11 and 14 months, respectively. Sixteen patients treated with radical surgery with curative aim including 2 patients treated with Whipple's procedure showed 11 months of median survival. Actuarial survival rates at 9 month for patients treated with radical surgery and those treated with bypass surgery alone were 69% and 0%, res-

pectively(Fig. 4).

3. Complications

None of the patients died of radiation related complications. Treatment break had to be interposed during the treatment because of nausea in 2 patients and generalized fatigue in one patient. However, those patients were able to complete their treatments without affecting total dose. One patient receiving greater than 5000 cGy developed duodenal ulcer at 13 month following radiation therapy. Another patient died of biliary sepsis which was attributed to benign strictures within the biliary tract.

DISCUSSION

The tumors of extrahepatic biliary system vary in their natural history to some extent, but it is evident that most of these patients die of the result of local-regional spread of cancer, even after curative local treatment¹⁴. In fact, patients in our series showed natural progression of this disease and most of the tumors tend to be locally aggressive with or without peritoneal seeding. Since distant metastases are uncommon, treatment should be directed towards these infradiaphragmatic sites of failure.

Some components of local failure are seen in 80% of patients with GB cancers^{7, 23}. The incidence of local nodal metastases ranges from 26 to 52%⁸. Liver involvement is seen in 52-65% of patients^{7, 24}. Peritoneal and omental involvement has been observed in 18-38% of patients^{8, 24} and is more common when tumor invades the peritoneal surface of the gall bladder. Kopelson et al. reported a 26% incidence of local failure in all EHBD cancers following complete surgical resection⁷. The incidence is much higher (59%) following resection of hepatic duct cancers. Data summarized from 11 series showed a 41% incidence of lymph node metastases and a 36% incidence of liver metastases⁷. Peritoneal involvement was seen in 9% of patients⁹. Abdominal skin recurrence has been reported in both GB and EHBD cancers^{7, 14, 23}.

Surgery has a diagnostic, palliative and, in some

cases, curative role in the management of EHBS tumors. Because of anatomical limitations and early spread to regional nodes and liver, curative surgery is attempted in only about 15% of patients, with a 5 year survival of 5% and operative mortality of 11-28%²⁵. Recent surgical literature does indicate a higher resectability rate⁴, but failure patterns reported by Kopelson et al. indicate the need for adjuvant treatment²³. Surgery also plays an important role in defining tumor volume for postoperative irradiation.

Radiation has been shown to provide palliation as well as an occasional cure in these patients^{11, 13, 14, 16, 18}. Radiation can be delivered externally, intracavitarily, and intraoperatively. As in our study, irradiation has been usually used in advanced stages of the tumor with little hope of a cure. If adjuvant irradiation is to provide any increase in survival, it should be used soon after curative resection. Smoron has shown that median survival was higher in patients receiving 4500 cGy¹². Our study has confirmed palliative role of irradiation as well as its potentially curative role.

Also there are few reports of the use of adjuvant irradiation for carcinoma of the GB. Pilepich and Lambert reported on two patients irradiated for tumors with serosal and lymphatic extent. At the time of report, one was alive without evidence of disease at 17 months; the other died of tumor one year of treatment¹¹.

Treadwell and Hardin reported on 41 patients with GB cancers incidentally found at cholecystectomy. Those receiving adjuvant radiation therapy showed a significant increase in survival over those not receiving adjuvant therapy. However, the survival benefit was lost with longer follow up²⁶. Vaitinen treated 7 patients with adjuvant radiotherapy after curative surgery, with a median survival of 63 months⁹. By comparison, 24 patients treated with surgery alone showed a considerably shorter median survival, 29 months. Mean survival for the two groups were almost identical, 49 and 48 months, respectively.

Early reports suggested excellent palliation and extended survival by the addition of external radiotherapy, with the possibility of occasional cure

for EHBD cancers^{7, 10, 11, 12}. Terblanche reported long term survival in 2 patients treated with T-tube intubation followed by external radiotherapy. Further, all patients surviving longer than 2 years had received external radiotherapy²⁷. Mittal et al. suggested improved survival for higher dose²⁸, patients receiving more than 4500 cGy showing a longer median survival (11 months) than patients receiving less than 4500 cGy (4 months). All patients who were without evidence of disease at more than one year had received the higher dose.

Patients in our study did have a microscopic or gross residual disease following surgery, although patients underwent curative surgery. Overall median survival periods were 11 months for GB cancers and 10 months for EHBD cancers. These results are similar to other reports and seem to be better than results reported in surgery alone series. Thus, patients who have high risk of residual disease after complete resection are likely to get benefit from adjuvant irradiation as reported by Fields et al.²⁹ Doses of 4500–5000 cGy to the tumor bed and regional lymph nodes are likely to provide loco-regional tumor control, and for some patients, cure.

CONCLUSION

Postoperative external beam radiotherapy for carcinoma of the gall bladder and extrahepatic bile duct is well tolerated and might improve survival of patients, especially those with resectable lesions with microscopic or gross residual disease after surgery.

REFERENCES

1. **Adson MA, Farnell MB.** Hepatobiliary cancer—surgical considerations. *Mayo Clin Proc* 1981; 56:686–699
2. **Bergdahl L.** Gallbladder carcinoma first diagnosed at microscopic examination of gallbladders removed for presumed benign disease. *Ann Surg* 1977; 112:26–30
3. **Chitwood WR, Myers WC, Heaston DK, et al.** Diagnosis and treatment of primary extrahepatic bile duct tumors. *Am J Surg* 1982; 143:99–106
4. **Evander A, Freudlund P, Hoevels J, Ihse I, Bengmark S.** Evaluation of aggressive surgery for carcinoma of the extrahepatic bile ducts. *Ann Surg* 1980; 191:23–29
5. **Fahim RB, Ferris DO, McDonald JR.** Carcinoma of the gallbladder. An appraisal of its surgical treatment. *Arch Surg* 1963; 86:334–341
6. **Fahim RB, McDonald JR, Richards JC, Ferris DO.** Carcinoma of the gallbladder. A study of its modes of spread. *Ann Surg* 1962; 156:114–124
7. **Kopelson G, Harisiadis L, Tretter P, Chang CH.** The role of radiation therapy in cancer of the extrahepatic biliary system. *Int J Radiat Oncol Biol Phys* 1977; 2:883–894
8. **Vattinen E.** Carcinoma of the gallbladder. A study of 390 cases diagnosed in Finland 1953–1967. *Ann Chir Gynaecol Fenn* 1970; 59:7–31
9. **Warren KW.** Malignant tumors of the bile ducts. *Br J Surg* 1972; 59:501–505
10. **Hanna SS, Rider WD.** Carcinoma of the gallbladder or extrahepatic bile ducts: The role of radiotherapy. *CMA J* 1978; 118:59–61
11. **Pilepich MV, Lambert PM.** Radiotherapy for carcinomas of the extrahepatic biliary system. *Radiology* 1978; 127:767–770
12. **Smoron GL.** Radiation therapy of carcinoma of gallbladder and biliary tract. *Cancer* 1977; 40:1422–1424
13. **Abe M, Takahasi M, Yabumoto E, Adachi H, Yoshi M, Mori K.** Clinical experiences with intraoperative radiotherapy of locally advanced cancers. *Cancer* 1980; 45:40–48
14. **Buskirk SJ, Gunderson LL, Adson MA, et al.** Analysis of failure following curative irradiation of gallbladder extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1984; 10:2013–2023
15. **Todoroki T, Iwasaki Y, Okamura T, et al.** Intraoperative radiotherapy for advanced carcinoma of the biliary system. *Cancer* 1980; 46:2179–2184
16. **Conroy RM, Shahbazian AA, Edwards KC, et al.** A new method for treating carcinomatous biliary obstruction with intracatheter radium. *Cancer* 1982; 49:1321–1327
17. **Fletcher MS, Brinkley D, Dawson JL, Nunnerly H, Williams R.** Treatment of hilar carcinoma by bile drainage combined with internal radiotherapy using iridium wire. *Br J Surg* 1983; 70:733–735
18. **Hershkovic AM, Engler MJ, Noell KT.** Radical radiotherapy for bile duct carcinoma. *Endocr Hyperth Oncol* 1985; 1:119–124

19. **Johnson DW, Safai C, Goffinet DR.** Malignant obstructive jaundice: Treatment with external beam and intracavitary radiotherapy. *Int J Radiat Oncol Biol Phys* 1985; 11:411-416
20. **Molt P, Hopfan S, Watson RC, Botet JF, Brennan MF.** Intraluminal radiation therapy in the management of malignant biliary obstruction. *Cancer* 1986; 57:536-544
21. **Mornex F, Ardiet JM, Bret P, Jerard JP.** Radiotherapy of high bile duct carcinoma using intracatheter iridium wire. *Cancer* 1984; 54:2069-2073
22. **Prempree T, Cox EF, Sewchand W, Tang CK.** Cholangiocarcinoma: A place for brachytherapy. *Acta Radiol Oncol* 1983; 22:353-359
23. **Kopelson G, Gunderson LL.** Primary and adjuvant radiation therapy in gallbladder and extrahepatic biliary carcinoma. *J Clin Gastroenterol* 1983; 5:43-50
24. **Glenn F, Hays DM.** The scope of radical surgery in the treatment of malignant tumors of the extrahepatic biliary tract. *Surg Gynecol Obstet* 1959; 99:529-541
25. **Akwari OE, Kelly KA.** Surgical treatment of adenocarcinoma. *Arch Surg* 1979; 114:22-25
26. **Treadwell TA, Hardin WJ.** Primary carcinoma of the gallbladder. The role of adjunctive therapy in its treatment. *Am J Surg* 1976; 132:703-706
27. **Terblanche J.** Carcinoma of the proximal extrahepatic biliary tree. Definitive and palliative treatment. *Surg Annu* 1979; 11:249-265
28. **Mittal B, Deutsch M, Iwatsuki J.** Primary cancers of the extrahepatic biliary passages. *Int J Radiat Oncol Biol Phys* 1985; 11:849-854
29. **Fields JN, Emami B.** Carcinoma of the extrahepatic biliary system—results of primary and adjuvant radiotherapy. *Int J Oncol Biol Phys* 1987; 13:331-338

= 국문초록 =

담낭 및 간의 담도계암의 방사선 치료성적

한양대학교 의과대학 치료방사선과학교실

전 하 정 · 이 명 자

목 적 : 담낭과 간의 담도를 포함한 간의 담도계암에 대한 방사선치료의 효과를 평가하고 방사선치료의 역할에 관하여 알아보고자 함이 본 연구의 목적이다.

대상 및 방법 : 1986년 4월에서 1994년 7월까지 본원 치료방사선과에서 외부 방사선치료를 받은 43명의 담낭 및 간의 담도계암 환자를 후향적으로 분석하였다. 23명은 담낭암이었고 20명은 간의 담도암이었다. 23명의 담낭암 환자중에서 제 2병기는 2명, 제 3 병기는 12명, 제 4병기는 9명이었다. 남녀비는 11명대 12명이었다. 15명은 근치적 절제술을 시행하였고, 8명은 조직생검과 우회수술만을 시행하였다. 3명을 제외한 모든 환자에서 수술후 4500 cGy 이상의 방사선을 조사하였으며, 추적기간은 11-82개월 이었다. 20명의 간의 담도암 환자중에서 제 1병기는 1명, 제 2병기는 2명, 제 3병기는 10명, 제 4병기는 7명이었다. 남녀비는 16명대 4명이었다. 16명이 근치적 목적으로 위플씨 수술 또는 절제와 배액술을 시행하였고, 나머지 4명은 우회수술만을 시행하였다. 16명은 수술후 방사선 치료로 4500 cGy 이상 조사하였고, 4명은 3180-4140 cGy를 조사하였다. 추적기간은 8-34개월 이었다.

결 과 : 담낭암 환자의 전체 중앙 생존기간은 11개월이었다. 제 3병기와 제 4병기의 중앙 생존기간은 14개월과 5개월이었으며, 2년 생존율은 각각 36%(4/11)와 13%(1/8) 이었다. 근치적 목적으로 수술을 받은 환자들보다 위플씨 수술 만으로 치료받은 환자들보다 통계적으로 유의하게 생존율이 높았다.(67% : 13% 12개월) 치료와 연관된 합병증으로 사망한 환자는 없었다. 20명의 간의 담도암 환자의 전체 중앙 생존기간은 10개월이었다. 제 3병기 10명과 제 4병기 7명의 중앙 생존기간은 각각 10개월과 8개월이었다. 위플씨 수술을 시행한 2명은 각각 11개월과 14개월 간 생존하였으며, 절제와 배액술로 치료한 환자들의 중앙 생존기간은 10개월이었다.

결 론 : 간의 담도계암 환자에서 수술후 외부 방사선치료에 의한 합병증은 미미하였으며, 특히 수술후 현미경적 또는 육안적 잔여병변이 있는 환자에서 방사선 치료에 의해 생존율이 증가하는 양상을 나타내었다.