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Originalarbeit

Adjuvant Radiotherapy after Radical Hysterectomy of the Cervical Cancer

Prognostic Factors and Complications

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Aim: To investigate prognostic factors and complications after radical hysterectomy followed by postoperative radiotherapy for carcinoma of the uterine cervix.
Patients and Methods: One hundred twenty-eight patients with Tlb-2b carcinoma of the uterine cervix following radical hysterectomy with bilateral pelvic lymphadenectomy and postoperative radiation therapy were reviewed. Pathologic and treatment variables were assessed by multivariate analysis for local recurrence, distant metastases and cause specific survival.
Results: The number of positive nodes (PN) in the pelvis was the strongest predictor of pelvic recurrence and distant metastases. These 2 failure patterns independently affect the cause specific survival. The 5-year cumulative local and distant failure were PN(0): 2% and 12%, PN(1–2): 23% and 25%, PN(2<): 32% and 57%, respectively ($p = 0.0029$ and $p = 0.0051$). The 5-year cause specific survival rates were PN(0): 90%, PN(1–2): 59% and PN(2<): 42% ($p = 0.0001$). The most common complication was lymphedema of the foot experienced by one-half of the patients (5-year: 42%, 10-year: 49%).
Conclusion: These results suggest that patients with pathologic Tlb–T2b cervix cancer with pelvic lymph node metastases are at high risk of recurrence or metastases after radical hysterectomy with pelvic lymphadenectomy and postoperative irradiation.

Key Words: Postoperative radiotherapy · Cervical cancer · Prognostic factors

Adjuvante Radiotherapie nach radikaler Hysterektomie bei Zervixkarzinom – Prognostische Faktoren und Komplikationen

Ziel: Untersuchung der prognostischen Faktoren und Komplikationen der adjuvanten Radiotherapie nach radikaler Hysterektomie bei Patienten mit Zervixkarzinom.
Patienten und Methoden: In dieser Studie wurden 128 Patientinnen mit Zervixkarzinom untersucht, bei denen die pathologische Untersuchung nach radikaler Hysterektomie mit gleichzeitiger bilateraler pelvischer Lymphadenektomie und postoperativer Radiotherapie die Klassifikation als Tlb–T2b-Karzinome ergab. Dabei wurden pathologische und therapeutische Parameter auf der behandelten Seite mit Hilfe der Multivarianzanalyse auf lokale Rezidive und Fernmetastasen beeinflussende Faktoren hin untersucht.
Ergebnisse: Die Zahl der metastatischen pelvischen Lymphknoten (PN) war der wichtigste Indikator fur die Wahrscheinlichkeit für das Auftreten von lokalen Rezidiven und Fernmetastasen, wobei beide Parameter die Überlebensrate der Grundkrankheit fast unabhängig voneinander beeinflußten. Die kumulativen Fünf-Jahres-Raten für lokale Rezidive und Fernmetastasen waren jeweils bei PN(0): 2% und 12%, PN(1–2): 23% und 25% und PN(2<): 32% und 57% ($p = 0{,}0029$ und $p = 0{,}0051$). Die Fünf-Jahres-Überlebensraten für die Grundkrankheit waren jeweils bei PN(0): 90%, PN(1–2): 59%, PN(2<): 42% ($p = 0{,}0001$). Die häufigste Komplikation waren Lymphödeme der Füße, die bei etwa der Hälfte der Patienten auftraten (fünf Jahre: 42%, zehn Jahre: 49%).
Schlußfolgerungen: Diese Ergebnisse deuten darauf hin, daß bei Patientinnen mit pathologisch als Tlb–T2b klassifizierten Zervixkarzinomen mit Lymphknotenmetastasen ein hohes Risiko von Rezidiven oder Metastasen nach radikaler Hysterektomie mit pelvischer Lymphadenektomie und postoperativer Bestrahlung besteht.

Schlüsselwörter: Postoperative Radiotherapie · Zervixkarzinom · Prognostische Faktoren

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In early stage carcinoma of the cervix, the presence of pelvic lymph node metastases has been associated with increased pelvic recurrence and distant metastases, and a decrease in overall survival. Whole pelvic irradiation attempts to improve survival for these patients, and the benefit of such therapy is demonstrated by several studies [4, 18]. The purpose of this study is to evaluate the prognostic factors for local control and survival in patients with carcinoma of the uterine cervix after radical hysterectomy and postoperative radiotherapy.

Patients and Methods

From April 1978 through August 1993, a total of 202 patients with carcinoma of the uterine cervix received postoperative radiation therapy. Of these 202 patients, 3 patients showed para-aortic lymph node metastases, 8 patients were pathologic T3, 22 patients received prophylactic para-aortic irradiation and 41 patients received simple hysterectomy without lymph-adenectomy. The remaining 128 patients, who received radical hysterectomy with lymph-adenectomy were pathologic Tlb-2b and received postoperative radiation therapy, constitute the subject of the present study.

Postoperative external irradiation was given to the pelvis by using 2 opposing anterior and posterior parallel fields with a 10-MV X-ray machine. Depending on the treatment period and pathologic findings 3 different treatment fields were followed, i. e., whole pelvis (27 cases), central shield field (34) and combination with whole pelvis and central shield field (67). The upper margin of the radiation field for whole pelvis included the upper border of the 5th lumbar vertebra, lower margin inferior border of pubic symphysis, and lateral margin at 2 cm lateral to the bony pelvis. In the central shield field the lower 2 thirds on the Y-axis of the whole pelvis field was blocked with a 4 cm shielded width. Treatment was given at 2 Gy per fraction. Total dose was 50 Gy in 5 weeks. The patients with microscopic tumor in the margin of the vaginal cuff resection received 20 Gy whole pelvis irradiation following 30 Gy by central shield field and high dose rate remote afterloading system (HDR-RALS) of 30 Gy/6 fractions/6 weeks at 5 mm depth with a vaginal cylinder. HDR-RALS was generally started with central shield field. Patients with no microscopic tumor present in the margin of the vaginal cuff resection received 50 Gy by whole pelvis irradiation or 50 Gy by central shield field with 25 Gy/5 fractions/5 weeks by HDR-RALS or a combination of 20 Gy to the whole pelvis following 30 Gy by central shield field with 25 Gy/5 fractions/5 weeks by HDR-RALS.

Prognostic factors were analyzed by Cox proportional linear hazard model as multivariate analysis [6]. The parameters included in these analyses were age, pathologic variables, i. e., histology, pathologic T stage, vaginal stump involvement, number of lymph node metastases, lymphatic space invasion, vascular space invasion, infiltration in the parametrium, extension to the uterine cavity and treatment variables, i. e., duration of the treatment time and treatment field.

Patient status was followed once a month for 1 year, then once every 3 months after radiation therapy. Clinical assessment, digital examination and WBC, hemoglobin, kidney and liver biochemical tests were performed at each examination. Once a year, chest X-ray, abdominal ultrasound and/or computed tomography were carried out. The overall follow-up period ranged from 2 months to 19.3 years (median: 7.1 years). Survival probability was calculated by Kaplan-Meier method [12] and statistical significance was determined by means of log-rank test [16]. Multiple independent statistical tests were performed by adjusting the p-value [2].

Site	No.
Local recurrence	
Pelvis	12
Vagina	4
Pelvis + vagina	2
Distant metastases	
Para-aortic lymph node	4
Supraclavicular lymph node	5
Para-aortic + supraclavicular lymph node	1
Bone	4
Skin	3
Lung	2
Others	4

Four cases showed local recurrence and distant metastases: vagina + skin 1; pelvic failure + skin 1; pelvic failure + bone 1; pelvic failure + para-aortic lymph node 1.

Table 1. First failure sites in 39 patients.

Tabelle 1. Lokale Rezidive und Fernmetastasen von 39 Patienten.

Results

Patterns of Failure

Patterns of failure were analyzed in 39 patients whose recurrent sites were evaluated at the time of last follow-up. The failure pattern was divided into local failure (18 cases) or distant metastases (25). Four patients showed both failure patterns. The sites of failure are described in Table 1. Failures in supraclavicular lymph nodes were considered to be accompanied by para-aortic lymph node metastases although 5 of 6 patients who showed supraclavicular lymph node metastases were not investigated because of their poor general condition.

Uni- and Multivariate Analyses for Local Recurrence, Distant Metastases and Survival

A univariate analysis was carried out to single out risk factors (Table 2). In that analysis no significant factor was found for local recurrence and distant metastases because only results within < 0.0019 can be considered to be significant, while in cause specific survival the number of lymph node metastases was the only significant prognostic factor in the univariate analysis. A multivariate analysis was performed using all prognostic factors. The number of positive nodes was the most significant factor in local recurrence, distant metastases and cause specific survival (Table 3). Cross tabulations with number of positive nodes and other pathologic variables were performed with each of the 7 items. The number of positive nodes correlated with lymphatic space invasion ($p = 0.006$), pathologic T stage ($p = 0.011$), endometrial invasion ($p = 0.036$) and a positive stump ($p = 0.045$), but did not correlate significantly with the other variables.

Prognostic factor	No. cases	Relative risk Local recurrence	Distant metastases	Prognostic factor	No. cases	Relative risk Cause specific survival
Age (years old)				Age (years old)		
28–50	58	1	1	28–50	58	1
51–72	70	0.315 (p=0.0368)	0.472 (p=0.0995)	51–72	70	0.483 (p=0.0466)
Pathology				Pathology		
Squamous cell ca.	107	1	1	Squamous cell ca.	107	1
Adenoca.	21	1.508 (p=0.5054)	3.573 (p=0.0363)	Adenoca.	21	1.325 (p=0.5400)
Pathologic T stage				Pathologic T stage		
T1b	40	1	1	T1b	40	1
T2a	20	0.912 (p=0.4832)	1.151 (p=0.1373)	T2a	20	1.013 (p=0.8530)
T2b	68	0.833	1.325	T2b	68	1.027
Vaginal stump				Vaginal stump		
-	106	1	1	-	106	1
+	22	1.061 (p=0.9354)	0.616 (p=0.4656)	+	22	1.132 (p=0.7997)
Lymph vessel involvment				Lymph vessel involvment		
-	66	1	1	-	66	1
+	62	1.398 (p=0.6044)	1.836 (p=0.2278)	+	62	0.993 (p=0.9869)
Vascular space involvment				Vascular space involvment		
-	101	1		-	101	1
+	27	3.128 (p=0.0841)	0.973 (p=0.9601)	+	27	1.560 (p=0.3443)
Extension in uterine cavity				Extension in uterine cavity		
-	114	1	1	-	114	1
+	14	0.279 (p=0.2450)	0.516 (p=0.3344)	+	14	0.631 (p=0.4229)
Infiltration in parametrium				Infiltration in parametrium		
-	60	1	1	-	60	1
+	68	3.805 (p=0.2688)	0.975 (p=0.9724)	+	68	1.388 (p=0.5921)
Lymph node metastases				Lymph node metastases		
0	62	1	1	0	62	1
1–2	43	2.270 (p=0.0368)	2.014 (p=0.0129)	1–2	43	2.470 (p=0.0002)
3–15	23	5.123	4.058	3–15	23	6.100
Treatment duration of irradiation (days)				Treatment duration of irradiation (days)		
34–42	54	1	1	34–42	54	1
43–49	40	0.902 (p=0.8009)	1.164 (p=0.6221)	43–49	40	1.063 (p=0.8130)
50–87	34	0.814	1.355	50–87	34	1.129
Radiation field				Radiation field		
WP+CS	67	1	1	WP+CS	67	1
Whole pelvis (WP)	27	1.623	1.236	Whole pelvis (WP)	27	1.314
Center shield (CS)	34	2.635 (p=0.1673)	1.527 (p=0.4475)	Center shield (CS)	34	1.725 (p=0.2322)

Table 2. Univariate analysis of prognostic factors: local control, distant metastases and cause specific survival.

Tabelle 2. Univariate Analyse von Prognosefaktoren: lokale Tumorkontrolle, Fernmetastasen und krankheitsspezifisches Überleben.

Prognostic factors	Relative risk	Significance
Local control by lymph node metastases		
0	1	
1–2	2.64 (1.53–4.54)	
3–15	6.95 (2.34–20.61)	0.0002
Distant metastases by lymph node metastases		
0	1	
1–2	2.48 (1.34–4.52)	
3–15	6.17 (1.86–7.39)	0.0015
Cause specific survival by lymph node metastases		
0	1	
1–2	2.21 (1.33–3.64)	

Table 3. Multivariate analysis of prognostic factors: local control, distant metastases and cause specific survival.

Tabelle 3. Multivariate Analyse von Prognosefaktoren: lokale Tumorkontrolle, Fernmetastasen und krankheitsspezifisches Überleben.

Cumulative Local Recurrence and Distant Metastases

Cumulative local recurrence rates and distant metastases were analyzed according to the number of positive nodes (PN) in pelvis and are shown in Figures 1 and 2. The 5-year cumulative local failure rates were PN(0): 2%, PN(1–2): 23% and PN(2<): 32%, respectively. The cumulative local recurrence rates were significantly different with number of positive nodes, i. e., PN(0) versus PN(1–2) p = 0.0018 and PN(0) versus PN(2c) p = 0.0002 but there was no significant difference between PN(1–2) versus PN(2<) (p = 0.9321).

The 5-year cumulative distant metastasis rates were PN(0): 12%, PN(1–2): 25% and PN(2<): 57%, respectively (Figure 3). The cumulative relapse rates were significantly different with number of lymph node metastases, i. e., PN(0) versus PN(2<) p = 0.0006 but no significant difference between PN(0) versus PN(1–2) (p = 0.0576) and PN(1–2) versus PN(2c) (p = 0.1520).

Cause Specific Survival

The 5-year cause specific survival rates were PN(0): 90%, PN(1–2): 59% and PN(2<): 42%, respectively. Concerning

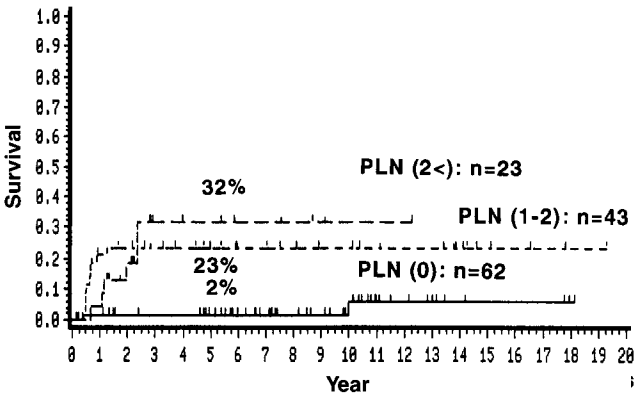

Figure 1. Cumulative local recurrence according to positive lymph node (PLN).

Abbildung 1. Die kumulativen lokalen Rezidive in Abhängigkeit von den metastatischen pelvischen Lymphknoten.

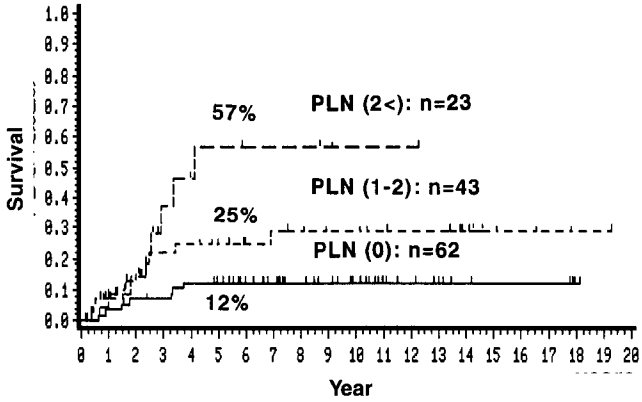

Figure 2. Cumulative distant metastases according to positive lymph node (PLN).

Abbildung 2. Die kumulativen Fernmetastasen in Abhängigkeit von den metastatischen pelvischen Lymphknoten.

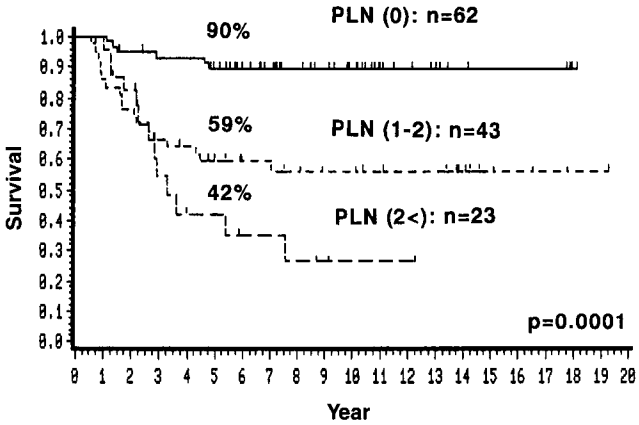

Figure 3. Cause specific survival according to positive lymph node (PLN).

Abbildung 3. Krankheitsspezifisches Überleben in Abhängigkeit von den metastatischen pelvischen Lymphknoten.

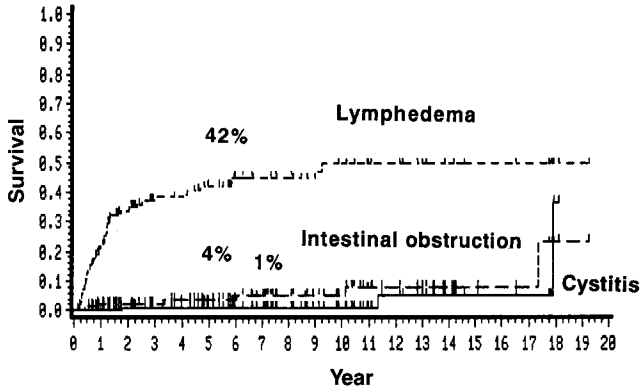

Figure 4. Cumulative chronic complication rate and time occurrence after radiation therapy.

Abbildung 4. Die kumulative Komplikationsrate in Abhängigkeit von der Gesamtbehandlungszeit.

the number of lymph node metastases, the cause specific survival was significantly different with a varied number of lymph node metastases, i. e., PN(0) versus PN(1–2) p = 0.0001, PN(0) versus PN(2c) p = 0.0001 but no significant difference between PN(1–2) versus PN(2c)(p = 0.1894).

Complications

Complications related to surgery and radiotherapy were observed in 60 patients. Three patients experienced more than one complication, i. e., lymphedema and intestinal complication (2 cases), lymphedema and bladder complication (1 case).

These complications were divided into 3 groups according to severity, i. e., Grade 1: mild symptoms; Grade 2: severe complications requiring medical treatment; Grade 3: those requiring surgical treatment.

Figure 4 shows the cumulative complication rates and time of occurrence after radiotherapy for bladder, intestinal complications and lymphedema. Complication rates for bladder and bowel were relatively low in incidence while lymphedema developed gradually until 10 years. The most common complication was lymphedema, experienced by one-half of the patients (5-year: 42%, 10-year: 49%). In general, the lymphedema was mild and tolerable except for 7 cases who required medical treatment with diuretics for edema (Table 4). Intestinal obstruction requiring medical treatment occurred in 4 patients and surgical treatment in 1 patient. Four of these 5 patients are alive and another recurred locally. Hemorrhagic cystitis was observed in 2 patients. There were no fatal toxicities among the entire group of 128 patients.

Complications	None	Grade 1	Grade 2	Grade 3
1) Lymphedema of the foot	83	46	7	0
2) Intestinal obstruction	142	2	4	1
3) Hemorrhagic cystitis	145	1	2	0

Three cases showed double complications: 1) + 2), 2 cases, 1) + 3), 1 case.

Table 4. Complications in 60 patients.

Tabelle 4. Komplikationsrate bei 60 Patienten.

Discussion

Pelvic radiation for patients with positive pelvic lymph nodes and other poor pathologic indicators has been used following radical hysterectomy as a standard treatment although prospective randomized trials have not been described. Conclusions cannot be drawn regarding the efficacy of adjuvant pelvic irradiation from some reports in the literature [3, 14]. Several retrospective studies, however, show the efficacy of adjuvant treatment. Bianchi et al. [4] treated 60 patients with external irradiation for pelvic node metastases after radical hysterectomy and observed a 65% 5-year survival rate. In contrast, in 15 patients who refused postoperative irradiation, only 3 survived 5 years. The improvement in survival was particularly noticeable in Stage II patients. Kinney et al. [11] retrospectively evaluated patients who were found to have pelvic nodal metastases at the time of radical hysterectomy and pelvic lymphadenectomy by matching irradiated and non-irradiated patients according to stage, tumor size, number and location of positive nodes. The pelvic recurrence rates for the surgery group (67%) versus the combined group (27%) were significant although the 5-year survival rates for the surgery group (72%) versus the combined group (64%) were not significant. Stock et al. [18] also reported that postoperative pelvic irradiation versus surgery alone significantly improves pelvic control, i. e., the combined group 78% versus the surgery group 45% ($p = 0.0004$), disease-free survival 65% versus 41% ($p = 0.0004$), and overall survival 58% versus 46% ($p = 0.02$), respectively.

Some factors such as stage, size of the tumor, histologic type and grade, cervical stromal invasion, growth into uterine corpus, patient's age and vascular invasion were shown to influence outcome [15]. But many investigators have shown that positive pelvic nodes were a more unfavorable factor. Gonzalez et al. [8] found that the 5-year survival rate in the group without lymph node metastases was 85% as compared to 60% with positive nodes. Similarly, Gerbaulet et al. [7] reported 89% 5-year survival in node negative patients in contrast with 55% 5-year survival rates in node-positive patients ($p < 0.0001$). In the series of Atkovar et al. [1], the 5-year disease-free survival rates for patients with and those without pelvic node metastases were 82.5% and 36.6% ($p = 0.0017$). In the present series, the 5-year cause specific survival rates were 90% in node-negative patients in contrast 59% with 1 to 2 positive nodes ($p = 0.0001$) and 42% in patients with more than 2 positive nodes ($p = 0.0001$). The number of positive nodes correlated with lymphatic space invasion, pathologic T stage, endometrial invasion and a positive stump.

Prophylactic para-aortic irradiation (PI) has also been used in the treatment of cervical cancer, because the para-aortic nodes represent the secondary drainage site after the pelvic lymph nodes. Prophylactic para-aortic irradiation might decrease para-aortic recurrence, distant metastases, and improve survival. A logical question would be whether this treatment would be beneficial in cases with known pelvic lymph node metastases and other risk factors. For prophylactic para-aortic lymph node irradiation, 2 major studies were conducted for the assessment of its advantages after radical irradiation of the cervix. RTOG conducted a comparable study on pelvic radiation in conjunction with pelvic plus para-aortic radiation therapy, using 367 patients with Stage IB, Stage IIA or Stage IIB tumors. The 2 groups in each treatment arm showed no significant differences in pelvic disease control or disease-free survival but an improved survival rate (PI+: 65% versus PI-: 55%; $p = 0.043$) and fewer distant metastases including para-aortic lymph nodes (PI+: 12% versus PI-: 22%; $p = 0.04$) [17]. EORTC has also reported the results of another comparable study on pelvic and para-aortic groups comprised of 441 patients with cervical carcinoma. Four-year disease-free survival rates of patients in the PI- and PI+ groups showed no significant difference (50% versus 53%) in spite of the low incidence of para-aortic lymph nodes recurrence in the PI+ arm [9]. In our small Phase III study [5] including radical radiotherapy and postoperative radiotherapy after radical hysterectomy, survival was essentially the same for both PI+ and PI- groups. The absence of pelvic control and hematogeneous spread of a tumor rather than the intensity of PI may have been a determining factor for survival.

Concerning the complications after radical hysterectomy following adjuvant radiotherapy, Morrow [14] noted no difference in the rate of serious complications compared with surgery alone. In our series, severe complications requiring surgical treatment were observed in 1 patient, i. e., intestinal obstruction seemed to be lower than that in other reported series [7, 14]. Lymphedema of the foot is not thought of as a serious complication and is rarely mentioned in reports dealing with treatment complications. Martimbeau et al. [13] reported that 23.4% of patients (94/402) developed lymphedema, and found no difference in the lymphedema rate among treatment modalities, i. e., lymphadenectomy with or without irradiation. Takamura et al. [19] reported that 56% of the 76 patients experienced mild to moderate lymphedema; this percentage is more than twice that reported by Morrow [14]. In our study, one-half of the patients (5-year: 42%, 10-year: 49%) developed Grade 1 to 2 lymphedema.

In conclusion, our study suggests that patients with pathologic Tlb–T2b cervical carcinoma after radical hysterectomy with pelvic lymph node metastases and postoperative pelvic irradiation would be more likely to have local recurrence, distant metastases and poor survival. Thus, in patients with positive lymph nodes postoperative radiation may be beneficial. In addition Phase III trials are needed concerning postoperative irradiation with or without adjuvant chemotherapy in these patients.

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