기관고유연구사업 최종보고서

(과제번호 : 1010480)

연구과제명 (국문) : 양성자선을 이용한 고형암치료의 새로운 응용 및 치료법 개발을 위한 전향적 임상연구

연구과제명 (영문) : Prospective clinical research for the development of new application and treatment using proton beam therapy for solid tumors

과제책임자 : 김 대 용

국 립 암 센 터

(뒷면)

1. 이 보고서는 국립암센터 기관고유연구사업 최종보고서입니다.
2. 이 보고서 내용을 인용할 때에는 반드시 국립암센터 연구사업 결과임을 밝혀야 합니다.

(측면)

양성자선을 이용한 고형암치료의 새로운 응용 및 치료법 개발을 위한 전향적 임상연구

제 출 문

국립암센터 원장 귀하

이 보고서를 기관고유연구사업 “양성자선을 이용한 고형암치료의 새로운 응용 및 치료법 개발을 위한 전향적 임상연구” 과제의 최종보고서로 제출합니다.

2012. 11. 01

국 립 암 센 터

과 제 책 임 자 : 김 대 용

목 차

< 요 약 문 >

(한글) 양성자선을 이용한 고형암치료의 새로운 응용 및 치료법 개발을 위한 전향적 임상연구

(영문) Prospective clinical research for the development of new application and treatment using proton beam therapy for solid tumors

< 요 약 문 >

연구분야(코드)			과제번호	1010480-3
과 제 명	양성자선을 이용한 고형암치료의 새로운 응용 및 치료법 개발을 위한 전향적 임상연구			
연구기간/연구비 (천원)	합계	2010년 01월 01일~2012년 12월 31일		240,000
	1차년도	2010년 01월 01일~2010년 12월 31일		80,000
	2차년도	2011년 01월 01일~2011년 12월 31일		80,000
	3차년도	2012년 01월 01일~2012년 12월 31일		80,000
과제책임자	성 명	김대용		
	소 속	양성자치료센터		
색인단어	국문	양성자치료, 새로운 응용		
	영문	Proton beam therapy, new application		

◆ 연구목표

<최종목표>

- 전향적 임상시험을 통한 고형암에 대한 양성자치료의 새로운 응용 및 치료법 개발

<당해년도 목표>

-기존 임상시험 지속 시행 및 개발

-개발된 프로토콜에 따른 임상자료의 수집

◆ 연구내용 및 방법

-획기적인 암 치료법으로 알려져 있는 양성자치료시설이 우리나라 최초로 국립암센터에 설치되어 2007년 3월 19일부터 환자치료에 적용하고 있음. 전향적 임상연구를 통하여 고형암종에 대한 양성자치료의 새로운 응용 및 치료법을 개발하여 암환자의 완치율을 높이고 삶의 질 향상에 기여함.

(1) 대표적 고형암에 대한 양성자치료를 이용한 임상시험의 시행 및 임상자료 수집

- 간세포암에서 호흡주기 추적 양성자치료를 이용한 I상 임상 연구 (등재완료)
- 척색종, 연골육종, 비정형 또는 악성 수막종에 대한 양성자치료의 1상 연구(환자등재완료, f/u중)
- 방사선 치료 후 재발한 척색종, 연골육종, 비정형 또는 악성 수막종에 대한 양성자치료의 1상 연구
- 전립선암에 대한 저분할 양성자치료의 2상 연구
- Prospective study of proton beam Craniospinal Radiotherapy in Children with Newly-Diagnosed Medulloblastoma-Assessment of Acute and Long Term Sequelae and quality of life
- 여성생식기암환자에서 대동맥림프절으로의 전이 및 재발병변의 양성자치료에 대한 효과연구

(2) 새로운 치료법 개발을 위한 임상시험의 기획

- 4개의 새로운 임상시험 개발

- 한국 소아 상의세포종의 치료에서 수술 후 양성자치료의 역할에 대한 전향적 연구 (2010년)
- 1기 비소세포성 폐암에서 로봇을 이용한 폐엽절제술과 저분할 양성자선 치료의 효과 비교에 대한 무작위 2상 임상 연구 (2010년)
- 소아 뇌종양에서 양성자를 이용한 Craniospinal radiotherapy (전뇌척수방사선치료)시 독성에 대한 비교연구 (Evaluation of the treatment-related toxicities of proton beam craniospinal radiotherapy (CSRT) in the patients with brain tumors) (2011년)
- 간세포암에 대한 저분할 양성자치료의 II상 임상연구 (2012년)

◆ 연구성과

-정량적 성과

구분	달성치/목표치[1)]	달성도(%)
SCI 논문 편수	10/6	167%
IF 합	31.481/24	131%
기타 성과		

1) 총연구기간내 목표 연구성과로 기 제출한 값

-정성적 성과

1) 양성자치료를 이용한 새로운 임상시험 프로토콜 개발

양성자치료에 관련된 10개의 프로토콜 중 4개의 프로토콜이 연구기간에 개발되어 환자 등재 중

2) 개발된 양성자치료를 이용한 프로토콜에 환자 등재 및 자료 수집

- 현재 개발된 프로토콜에 286명의 환자가 등재되어 있음.
- 세부 프로토콜의 환자 등재현황은 연구수행 내용 및 결과에서 보임.
- 임상연구는 환자 등재 후 수년간의 추적검사가 필요하여 단기간 내에 그 결과를 도출하기 어려움. 하지만 현재 3개의 프로토콜 NCCCTS-06-225, NCCCTS-07-244 : 등재완료, NCCCTS-07-253:등재 거의 완료되어, NCCCTS-07-244:manuscript 작성 중, NCCCTS-07-253:review 중으로 그 결과를 SCI 저널에 발표할 수 있을 것임.

3) 양성자 치료 진료 의뢰 및 상담을 위한 Hotline의 개설 및 운영

◆ 참여연구원 (최종연도 참여인원)	성 명	김대용, 조관호, 김주영, 신경환, 이세병, 신동호, 김상수, 김태현, 문성호, 김기홍, 양재석, 여승구, 김재은, 유소명, 신은하

※ 요약문의 총분량은 2page 이내로 제한함

Project Summary

Title of Project	Prospective clinical research for the development of new application and treatment using proton beam therapy for solid tumors
Key Words	Proton beam therapy, new application
Project Leader	Dae Yong Kim, M.D.
Associated Company	none

Photon (X-ray), a type of electromagnetic waves, exerts different physical properties from proton (particle). Photons deliver maximum radiation to the normal tissue in front of the target (tumor) and cannot stop once it has passed through target resulting in radiation exposure to normal tissue behind the target. Unlike photons, protons deliver maximum radiation to the target and stop right after they have passed the target resulting in no radiation exposure to normal tissue behind the target. Compared with photon, proton therapy, therefore, allows more radiation dose to the target while limiting the dose to the surrounding normal tissues. As a result, proton therapy can improve tumor control while minimizing side effects.

Our research interests are to quantify the clinical gains offered by this new treatment modality using protons through well-designed, prospective clinical trials. The primary goals of clinical research are as follows:

Category 1) To test the hypothesis that, in tumors with sub-optimal local control with photon therapy, the superior dose localization of proton therapy will allow increased tumor doses that will result in increased local control while maintaining treatment related morbidity and quality of life.

Category 2) To test the hypothesis that, in tumors with satisfactory local control, but with high treatment related morbidity with photon therapy, the superior dose localization of proton therapy will allow to decrease treatment related morbidity and to improve quality of life while maintaining current local control.

Based on this background, 10 prospective clinical protocols were developed. To date, 286 patients were enrolled into the protocols and were under follow-up. Patients' accruals are almost completed in some of the protocols including NCCCTS-06-225, NCCCTS-07-244, NCCCTS-07-253. It is writing a manuscript and reviewing from these clinical studies.

※ 연구목표, 연구방법, 연구성과를 영문으로 요약하여 2쪽이내의 분량으로 작성

1. 연구의 최종목표

(1) 최종목표 :

임상시험을 통한 고형암에 대한 양성자치료을 이용한 새로운 치료법 개발

(2) 연차별 목표 및 내용

구분	목표	내용 및 범위
1차년도 (2010.01 - 2010.12)	새로운 양성자치료 프로토콜의 개발	전립선암, 뇌종양, 두경부종양, 척색종, 수모세포종, 초기 유방암, 초기 폐암, 간세포암에 대한 과제의 양성자치료 프로토콜 개발예정임
	개발된 프로토콜에 따른 임상자료의 수집	담당연구간호사에 의해 자료를 수집하며, 자료에 대한 검증과정을 체계화할 예정임
2차년도 (2011.1 - 2011.12)	기존 임상시험 지속 시행 및 개발	개발된 과제의 임상시험의 지속 시행 및 소아고형암, 폐암에 대한 새로운 치료법과 기존 약물치료와 병용치료법 개발 예정임
	개발된 프로토콜에 따른 임상자료의 수집	담당연구간호사에 의해 자료를 수집하며, 자료에 대한 검증과정을 체계화, 분석에 대한 전문가의 투입 예정임
3차년도 (2012.1 - 2012.12)	기존 임상시험 지속 시행 및 개발	개발된 임상시험의 지속 시행 및 다른 고형암에 대한 새로운 치료법과 기존 약물치료, 표적치료제등과의 병용치료법 개발 예정임
	개발된 프로토콜에 따른 임상자료의 수집	담당연구간호사에 의해 자료를 수집하며, 자료에 대한 검증과정을 체계화, 분석에 대한 전문가의 투입 예정임

2. 연구의 내용 및 결과

(1) 연구의 추진 전략 및 방법

① 기존 임상시험 지속 시행 및 개발

개발된 6개 과제의 임상시험의 지속 시행 및 소아고형암, 폐암, 간세포암에 대한 4개의 새로운 치료법과 기존 약물치료와 병용치료법 개발.

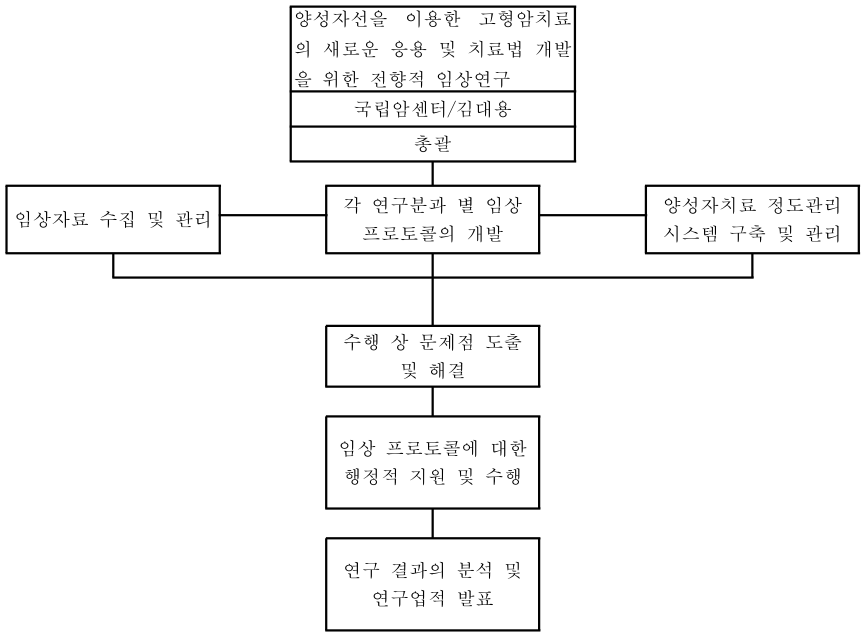
② 개발된 프로토콜에 따른 임상자료의 수집

담당 연구간호사에 의해 자료를 수집하며, 자료에 대한 검증과정을 체계화, 분석에 대한 전문가의 투입 예정임

③ 프로토콜 등재율 증진

양성자 치료를 이용한 임상시험을 홍보하고, 타 기관 연계 다기관 연구를 위한 임상연구 개발위해 학회 및 연구회 접속 중으로 타기관의 양성자 치료 진료 의뢰를 높여 임상시험의 등재율을 높일 예정임.

(2) 추진체계



(3) 신규 프로토콜 개발

<< 2010년도 >>

2개 신규 프로토콜을 본 기관 고유 사업의 프로토콜로 추가

■ 10-480 김주영 한국 소아 상의세포종의 치료에서 수술 후 양성자치료의 역할에 대한 전향적 연구

■ 10-494 조관호 1기 비소세포성 폐암에서 로봇을 이용한 폐엽절제술과 저분할 양성자치료의 효과 비교에 대한 무작위 2상 임상연구

<< 2011년도 >>

1개 신규 프로토콜 개발

■ 11-258 김주영 소아 뇌종양에서 양성자를 이용한 Craniospinal radiotherapy(전뇌척수 방사선치료)시 독성에 대한 비교 연구

<< 2012년도 >>

1개 신규 프로토콜 개발

■ 12-622 김태현 간세포암에 대한 저분할 양성자치료의 II상 임상연구

(4) 양성자치료를 이용한 임상시험의 시행 및 임상자료 수집 현황

Protocol No.	PI	프로토콜 이름	필요 증례수	현재 등재수	2010	2011	2012	등재율
06-225	김태현	간세포암에서 호흡주기 추적 양성자치료를 이용한 I상 임상연구	24	24	9	2	-	종료
07-243	조관호	방사선 치료 후 재발한 척색종, 연골육종, 비정형 또는 악성 수막종에 대한 양성자 치료의 1상 연구	24	13	0	5	0	54.2 %
07-244	조관호	척색종, 연골육종, 비정형 또는 악성 수막종에 대한 양성자 치료의 1상 연구	24	23	3	6	0	종료
07-247	김주영	Prospective study of proton beam Craniospinal Radiotherapy in Children with Newly-Diagnosed Medulloblastoma-Assessment of Acute and Long Term Sequelae and quality of life	37	15	1	6	6	40.5 %
07-253	조관호	전립선암에 대한 저분할 양성자 치료의 2상 연구	117	97	7	5	5	82.9 %
07-281	김주영	여성생식기암환자에서 대동맥림프절으로의 전이 및 재발병변의 양성자치료에 대한 효과연구	41	21	4	6	6	51.2 %
10-480	김주영	한국 소아 상의세포종의 치료에서 수술 후 양성자치료의 역할에 대한 전향적 연구	43	6	5	1	1	14%
10-494	조관호	1기 비소세포성 폐암에서 로봇을 이용한 폐엽절제술과 저분할 양성자치료의 효과 비교에 대한 무작위 2상 임상연구	110	54	1	36	18	49.1 %
11-528	김주영	소아 뇌종양에서 양성자를 이용한 Craniospinal radiotherapy(전뇌척수방사선치료)시 독성에 대한 비교 연구	58	24	-	13	11	41.4 %
12-622	김태현	간세포암에 대한 저분할 양성자 치료의 II상 임상연구	135	9	-	-	9	6.7%
합계			565	286	30	80	56	50.6 %

(5) 양성자치료 진료 의뢰 및 상담을 위한 Hotline 개설 및 운영

양성자치료 진료 의뢰와 상담을 위한 Hotline (031-920-1111)을 개설 및 운영하고 있다.

월 30~40회 정도의 양성자 치료 문의 전화를 처리하고 진료 예약을 위한 안내를 하고 있다.

3. 연구결과 고찰 및 결론

(1) 10개 프로토콜이 개발되어 현재까지 286명이 등재되어 추적검사 중임. 임상연구는 환자 등재 후 수년간의 추적검사가 필요하여 단기간 내에 그 결과를 도출하기 어려움. 하지만 현재 3개의 프로토콜 NCCCTS-06-225, NCCCTS-07-244 : 등재완료, NCCCTS-07-253:등재 거의 완료되어, NCCCTS-07-244:manuscript 작성 중, NCCCTS-07-253:review 중으로 그 결과를 SCI 저널에 발표할 수 있을 것임.

(2) 치료의 파라다임을 바꿀 수 있는 혁신적인 프로토콜 개발이 필요함. 현재 초기 폐암에서 수술을 대치 할 수 있는 양성자치료법을 개발하기 위해 로봇수술과 비교 연구가 개발되어 진행 중이나, 앞으로 더 많은 타 센터 및 타 전문분야와의 공동연구 및 협조가 필요함.

(3) 환자 등재 활성화: 양성자 치료는 비보험으로 치료비로 인한 환자등재에 어려움이 있음.
향후 치료비 보험 급여 추진 등으로 (현재 소아종양의 일부 종양에 한해서만 보험 적용중임) 환자 등재 활성화 필요함.

4. 연구성과 및 목표달성도

(1) 연구성과

가. 국내 및 국제 전문학술지 논문 게재 및 신청

논문명	저자 (저자구분[1])	저널명(I.F.)	Year; Vol(No):Page	구분[2]	지원과제번호[3]
Craniospinal Irradiation Techniques: A Dosimetric Comparison of Proton Beams with Standard and Advanced Photon Radiotherapy	윤명근 (제1)	Int J Radiat Oncol Biol Phys (4.105)	2011;81:637-46	국외 SCI	1010480 0910180
The effect of external beam radiotherapy volume on locoregional control in patients with locoregionally advanced or recurrent nonanaplastic thyroid cancer	김태현 (제1)	Radiation Oncology (2.231)	2010:5:69	국외 SCI	1010480
CA19-9 Level as an Indicator of Early Distant Metastasis and Therapeutic Selection in Resected Pancreatic Cancer	김태현 (제1)	Int J Radiat Oncol Biol Phys (4.105)	2011;81:e743-e748	국외 SCI	1010480
PRETREATMENT CARBOHYDRATE ANTIGEN 19-9 LEVEL INDICATES TUMOR RESPONSE, EARLY DISTANT METASTASIS, OVERALL SURVIVAL, AND THERAPEUTIC SELECTION IN LOCALIZED AND UNRESECTABLE PANCREATIC CANCER	김태현 (교신)	Int J Radiat Oncol Biol Phys (4.105)	2011;81:e623-e630	국외 SCI	1010480
ROLE OF ADJUVANT CHEMORADIOTHERAPY FOR RESECTED EXTRAHEPATIC BILIARY TRACT CANCER	김태현 (제1)	Int J Radiat Oncol Biol Phys (4.105)	2011;81:e853-e859	국외 SCI	1010480
Clinical Outcomes of Chemoradiotherapy for Locally Recurrent Rectal Cancer	김대용 (교신)	Radiation Oncology (2.231)	2011; 6:51	국외 SCI-E	1010480 0910010
THE EFFECT OF A CONTRAST AGENT ON PROTON BEAM RANGE IN RADIOTHERAPY PLANNING USING COMPUTED TOMOGRAPHY FOR PATIENTS WITH LOCOREGIONALLY ADVANCED LUNG CANCER	김태현 (교신)	Int J Radiat Oncol Biol Phys (4.105)	2011;81:e317-e324	국외 SCI	1010480 0910210
Phase 3 Trial of Postoperative Chemotherapy Alone Versus Chemoradiation Therapy in Stage III-IV Gastric Cancer Treated With R0 Gastrectomy and D2 Lymph Node Dissection	김대용 (교신)	Int J Radiat Oncol Biol Phys (4.105)	2012 Epub	국외 SCI	1010480
Curative Radiotherapy for Isolated Lung Metastasis from Colorectal Cancer	김대용 (교신)	Tumori (0.606)	2012 accepted	국외 SCI	1010480 0910010
Stage-to-stage Comparison of Neoadjuvant Chemotherapy Versus Adjuvant Chemotherapy in Pathological Lymph Node Positive Breast Cancer Patients: Japanese Journal of Clinical Oncology. Online:Published	신경환 (교신)	JJCO (1.783)	2012 Epub	국외 SCI-E	1010480

1) 저자구분 : 교신, 제1, 공동
2) 구분 : 국내, 국내 SCI, 국내 SCIE, 국외, 국외SCI, 국외SCIE 등
3) 지원과제번호(Acknowledgement)
- 과제번호를 연차 표시(-1, -2, -3 등)를 생략하고 7자리로 기재하고, 과제와 관련성은 있으나 불가피하게 Acknowledgement가 누락된 경우에는 '없음'으로 기재

(2) 목표달성도

가. 연구목표의 달성도

최종목표	연차별목표		달성내용	달성도(%) 연차	달성도(%) 최종
전향적 임상시험을 통한 고형암에 대한 양성자치료의 새로운 응용 및 치료법 개발	1차년도 (2010.01 - 2010.12)	새로운 양성자치료 프로토콜의 개발	2개의 새로운 프로토콜 개발함. 소아암: 한국 소아 상의세포종의 치료에서 수술 후 양성자치료의 역할에 대한 전향적 연구 초기 폐암: 1기 비소세포성 폐암에서 로봇을 이용한 폐엽절제술과 저분할 양성자선 치료의 효과 비교에 대한 무작위 2상 임상연구	100	30
		개발된 프로토콜에 따른 임상자료의 수집	담당연구간호사에 의해 자료를 수집하며, 자료에 대한 검증과정을 체계화함		
	2차년도 (2011.1 - 2011.12)	기존 임상시험 지속 시행 및 개발	개발된 과제의 임상시험의 지속 시행 및 소아암의 새로운 프로토콜 개발함. - 소아 뇌종양에서 양성자를 이용한 Craniospinal radiotherapy (전뇌척수방사선치료)시 독성에 대한 비교연구(Evaluation of the treatment-related toxicities of proton beam craniospinal radiotherapy(CSRT) in the patients with brain tumors)	100	70
		개발된 프로토콜에 따른 임상자료의 수집	담당연구간호사에 의해 자료를 수집하며, 자료에 대한 검증과정을 체계화함		
	3차년도 (2012.1 - 2012.12)	기존 임상시험 지속 시행 및 개발	개발된 임상시험의 지속 시행 및 간세포암의 새로운 프로토콜 개발함. - 간세포암에 대한 저분할 양성자치료의 II상 임상연구	100	100

		개발된 프로토콜에 따른 임상자료의 수집	담당연구간호사에 의해 자료를 수집하며, 자료에 대한 검증과정을 체계화함		

나. 평가의 착안점에 따른 목표달성도에 대한 자체평가

평가의 착안점	자 체 평 가
기존 임상시험 지속 시행 및 개발	● 2010년도 2개, 2011년도 1개, 2012년도 1개의 신규 프로토콜이 개발되었음. ● 고형암에 대한 양성자치료를 이용한 10개의 임상시험이 개발되어 시행되고 있음.
개발된 프로토콜에 따른 임상자료의 수집	● 현재 총 50.6%의 환자 등재율을 보이고 있음. ● 담당 연구 간호사에 의해 자료를 수집하고 있으며, 자료에 대한 검증과정을 체계화 할 예정임

5. 연구결과의 활용계획

(1) 연구종료 2년후 예상 연구성과

구 분	건 수	비 고
학술지 논문 게재	6	J Clin Oncol (18.372), Int J Radiat Oncol Biol Phys (4.105) 등 impact factor 총합 24 이상
산업재산권 등록		특허 등록 예상 국가, 예상 특허명 등
기 타		

(2) 연구성과의 활용계획

가. 진료적인 측면

1) 고형암에서 양성자치료를 이용한 새로운 치료법을 개발하여 암환자의 생존율 증가 및 삶의 질 개선
2) 고형암 암종 및 병기별 양성자치료의 표준지침 마련

나. 지식 및 기술적 측면

1) 임상시험을 통한 양성자치료를 받은 환자의 Database를 구축
2) 고형암 암종 및 병기별에 따른 양성자치료, 방사선 민감제, 항암제 및 표적치료제을 이용한 새로운 치료법 개발
3) 논문 발표를 통하여 세계적인 암 진료 및 치료 기관으로서의 위상을 높임

다. 산업적 측면

1) 고형암의 양성자치료, 방사선 민감제, 항암제 및 표적 치료제를 이용한 새로운 치료법 개발
2) 국내 유수 기관 및 해외 기관들과의 연계를 통한 새로운 세계적인 임상시험에 참여기회를 확대

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7. 첨부서류

<논문 게재>

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CLINICAL INVESTIGATION **Brain**

CRANIOSPINAL IRRADIATION TECHNIQUES: A DOSIMETRIC COMPARISON OF PROTON BEAMS WITH STANDARD AND ADVANCED PHOTON RADIOTHERAPY

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Purpose: To evaluate the dosimetric benefits of advanced radiotherapy techniques for craniospinal irradiation in cancer in children.
Methods and Materials: Craniospinal irradiation (CSI) using three-dimensional conformal radiotherapy (3D-CRT), tomotherapy (TOMO), and proton beam treatment (PBT) in the scattering mode was planned for each of 10 patients at our institution. Dosimetric benefits and organ-specific radiation-induced cancer risks were based on comparisons of dose–volume histograms (DVHs) and on the application of organ equivalent doses (OEDs), respectively.
Results: When we analyzed the organ-at-risk volumes that received 30%, 60%, and 90% of the prescribed dose (PD), we found that PBT was superior to TOMO and 3D-CRT. On average, the doses delivered by PBT to the esophagus, stomach, liver, lung, pancreas, and kidney were 19.4 Gy, 0.6 Gy, 0.3 Gy, 2.5 Gy, 0.2 Gy, and 2.2 Gy for the PD of 36 Gy, respectively, which were significantly lower than the doses delivered by TOMO (22.9 Gy, 4.5 Gy, 6.1 Gy, 4.0 Gy, 13.3 Gy, and 4.9 Gy, respectively) and 3D-CRT (34.6 Gy, 3.6 Gy, 8.0 Gy, 4.6 Gy, 22.9 Gy, and 4.3 Gy, respectively). Although the average doses delivered by PBT to the chest and abdomen were significantly lower than those of 3D-CRT or TOMO, these differences were reduced in the head-and-neck region. OED calculations showed that the risk of secondary cancers in organs such as the stomach, lungs, thyroid, and pancreas was much higher when 3D-CRT or TOMO was used than when PBT was used.
Conclusions: Compared with photon techniques, PBT showed improvements in most dosimetric parameters for CSI patients, with lower OEDs to organs at risk.

Secondary cancer risk, Organ equivalent dose, Proton, Tomotherapy.

INTRODUCTION

Patients with brain tumors at risk of dispersion through the cerebrospinal fluid often require craniospinal irradiation (CSI), a complex technique in which orthogonal junctions are created between the lateral brain fields and a posterior spinal field (1–5). These technical difficulties can be resolved using three-dimensional conformal radiotherapy (3D-CRT), in which the patient is usually placed in the prone position, and careful junctions are created between opposed lateral cranial fields and a posterior spinal field. One major disadvantage of 3D-CRT is that large areas of normal tissue and organs at risk (OARs) in the vicinity of the target are also irradiated (6–10). In general, many patients requiring CSI treatment are children, in whom radiotherapy is frequently associated with severe side effects, such as endocrine and fertility dysfunctions, growth and musculoskeletal abnormalities, neurobehavioral deficits, and secondary malignancies.

Novel radiation technologies have been developed for large and complex targets to overcome the disadvantages of 3D-CRT. New technologies in the delivery of radiation therapy have included the use of intensity-modulated radiotherapy (IMRT) in linear accelerator (LINAC) or in helical tomotherapy (TOMO) and proton beam treatment (PBT), which have increased the ability to maximize the dose to the tumor but which spare normal structures (11–17). TOMO may be more useful than LINAC-based IMRT in the treatment of CSI patients, because helical delivery of the intensity-modulated fan beam allows treatment of extended volumes in the cranio-caudal direction, with the

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Conflict of interest: none.
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RADIATION ONCOLOGY

RESEARCH Open Access

The effect of external beam radiotherapy volume on locoregional control in patients with locoregionally advanced or recurrent nonanaplastic thyroid cancer

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Abstract

Purpose: We evaluated outcomes of patients treated with external beam radiotherapy (EBRT) for locoregionally advanced or recurrent nonanaplastic thyroid cancer and analyzed the effect of EBRT volume on locoregional control.

Methods: This study included 23 patients with locoregionally advanced or recurrent nonanaplastic thyroid cancer who were treated with EBRT. Two different EBRT target volumes were executed as follows: 1) limited field (LF, n = 11) included the primary (involved lobe) or recurrent tumor bed and the positive nodal area; 2) elective field (EF, n = 12) included the primary (involved lobe) or recurrent tumor bed and the regional nodal areas in the cervical neck and upper mediastinum. Clinical parameters, such as gender, age, histologic type, recurrence, stage, thyroglobulin level, postoperative residuum, radioiodine treatment, and EBRT volume were analyzed to identify prognostic factors associated with locoregional control.

Results: There were no significant differences in the clinical parameter distributions between the LF and EF groups. In the LF group, six (55%) patients developed locoregional recurrence and three (27%) developed distant metastasis. In the EF group, one (8%) patient developed locoregional recurrence and one (8%) developed a distant metastasis. There was a significant difference in locoregional control rate at 5 years in the LF and EF groups (40% vs. 89%, $p = 0.041$). There were no significant differences in incidences of acute and late toxicities between two groups ($p > 0.05$).

Conclusions: EBRT with EF provided significantly better locoregional control than that of LF; however, further larger scaled studies are warranted.

Introduction

Surgical resection, radioactive iodine treatment (RAI), and thyroid-stimulating hormone suppression are considered as standard treatments for nonanaplastic thyroid cancer. However, the role of external beam radiotherapy (EBRT) remains controversial. Despite conflicting data [1-4], a number of retrospective studies have demonstrated that EBRT potentially improves locoregional control in patients with nonanaplastic thyroid cancer who have high risk features for locoregional recurrence, such as pT4, lymph node involvement, micro-/macroscopic positive surgical margins, extensive extrathyroidal or extranodal extension at recurrence, or RAI-resistant recurrent disease [5-16]. To date, the current indication, radiation dose, and irradiated volume of EBRT have largely been determined from retrospective data.

Theoretically, EBRT is directed to the thyroid bed and draining lymphatics in the cervical neck and upper mediastinum to achieve locoregional control and it is recommended [17,18]. But, in clinical practice, EBRT volume

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CLINICAL INVESTIGATION **Pancreas**

CA 19-9 LEVEL AS INDICATOR OF EARLY DISTANT METASTASIS AND THERAPEUTIC SELECTION IN RESECTED PANCREATIC CANCER

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Purpose: In patients with pancreatic cancer treated with curative resection, we evaluated the effect of clinicopathologic parameters on early distant metastasis within 6 months (DM^{6m}) to identify patients who might benefit from surgery.

Methods and Materials: The study involved 84 patients with pancreatic cancer who had undergone curative resection between August 2001 and April 2009. The parameters of gender, age, tumor size, histologic differentiation, T classification, N classification, pre- and postoperative carbohydrate antigen (CA) 19-9 level, resection margin, and adjuvant chemoradiotherapy were analyzed to identify the risk factors associated with DM^{6m}.

Results: Of the 84 patients, locoregional recurrence developed in 35 (41.7%) and distant metastasis in 58 (69%). Of the 58 patients with distant metastasis, DM^{6m} had developed in 27 (46.6%). Multivariate analysis showed that preoperative CA 19-9 level was significantly associated with DM^{6m} ($p < .05$). Of all 84 patients, DM^{6m} was observed in 9.1%, 50%, and 80% of those with a preoperative CA 19-9 level of ≤100 U/mL, 101–400 U/mL, and >400 U/mL, respectively ($p < .001$).

Conclusions: The preoperative CA 19-9 level might be a useful predictor of DM^{6m} and to identify those who would benefit from surgical resection. © 2011 Elsevier Inc.

Pancreatic cancer, Distant metastasis, Carbohydrate antigen 19-9, CA 19-9.

INTRODUCTION

In pancreatic cancer, complete resection is still the only treatment option that can offer the hope of cure or long-term survival if patients do not have any distant disease. However, the 5-year overall survival rate of patients with resectable pancreatic cancer has been <25% because distant and locoregional failure develops in about 70% and 30% of patients, respectively, even after curative resection followed by chemotherapy and radiotherapy (RT) (1–5). Despite recent advances in diagnostics and therapeutics, significant numbers of patients still develop recurrent disease immediately after curative resection and/or adjuvant chemotherapy and RT, indicating the high probability of occult metastatic disease at diagnosis. Thus, a more effective surrogate marker to identify those patients most likely to benefit from surgery is needed.

Carbohydrate antigen (CA) 19-9, which was isolated from a human colorectal cancer cell line by Koprowski *et al.* (6) in 1979, has been used for the diagnosis, prognosis, and monitoring of patients with pancreatic cancer (7–14). Additionally, the serum pre- and postoperative CA 19-9 levels have been demonstrated to be independent predictors of recurrence and survival after resection (8–10, 15) and might correlate with the tumor burden, disease spread, and metastasis. Thus, in the present study, we examined the patterns of disease recurrence in patients with pancreatic carcinoma treated with curative resection and evaluated the effect of the clinicopathologic parameters on overall survival and early distant metastasis (*i.e.,* immediate distant failure within 6 months after curative resection). We also explored the clinical usefulness of the CA 19-9 level as a predictor of early distant metastasis.

METHODS AND MATERIALS

Patients

Between August 2001 and April 2009, 130 consecutive patients with pancreatic adenocarcinoma underwent curative resection at the National Cancer Center, Korea. Of the 130 patients, 46

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CLINICAL INVESTIGATION **Pancreas**

PRETREATMENT CARBOHYDRATE ANTIGEN 19-9 LEVEL INDICATES TUMOR RESPONSE, EARLY DISTANT METASTASIS, OVERALL SURVIVAL, AND THERAPEUTIC SELECTION IN LOCALIZED AND UNRESECTABLE PANCREATIC CANCER

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Purpose: The use of chemoradiotherapy (CRT) for localized and unresectable pancreatic cancer has been disputed because of high probability of distant metastasis. Thus, we analyzed the effect of clinical parameters on tumor response, early distant metastasis within 3 months (DM^{3m}), and overall survival to identify an indicator for selecting patients who would benefit from CRT.

Methods and Materials: This study retrospectively analyzed the data from 84 patients with localized and unresectable pancreatic cancer who underwent CRT between August 2002 and October 2009. Sex, age, tumor size, histological differentiation, N classification, pre- and post-treatment carbohydrate antigen (CA) 19-9 level, and CA 19-9 percent decrease were analyzed to identify risk factors associated with tumor response, DM^{3m}, and overall survival.

Results: For all 84 patients, the median survival time was 12.5 months (range, 2–31.9 months), objective response (complete response or partial response) to CRT was observed in 28 patients (33.3%), and DM^{3m} occurred in 24 patients (28.6%). Multivariate analysis showed that pretreatment CA 19-9 level (≤400 vs. >400 U/ml) was significantly associated with tumor response (45.1% vs. 15.2%), DM^{3m} (19.6% vs. 42.4%), and median overall survival time (15.1 vs. 9.7 months) ($p < 0.05$ for all three parameters).

Conclusion: For patients with localized and unresectable pancreatic cancer, pretreatment CA 19-9 level could be helpful in predicting tumor response, DM^{3m}, and overall survival and identifying patients who will benefit from CRT. © 2011 Elsevier Inc.

Pancreatic cancer, Overall survival, Distant metastasis, CA 19-9, Chemoradiotherapy.

INTRODUCTION

In pancreatic cancer, surgical resection is the only possibility of cure, but only 10% to 15% of patients have localized and resectable disease at diagnosis. Approximately 50% of pancreatic cancer patients present with distant metastatic disease, and 30% present with localized and unresectable disease. The prognosis of pancreatic cancer patients with localized and unresectable disease has remained poor because of high both local progression and distant metastasis, despite treatment with chemotherapy, radiotherapy (RT), or chemoradiotherapy (CRT), and optimal treatment for these patients remains controversial (1–5). It has reported that approximately 30% of patients with localized disease based on radiographic studies may actually have occult metastatic disease at laparoscopy (6). Furthermore, a fraction of these patients developed distant metastases within a few months and died very quickly despite treatment (7, 8). Thus, the use of CRT for patients with localized and unresectable disease has been disputed, because these patients usually die of distant metastases. Conversely, other studies showed that 30% to 55% of pancreatic cancer deaths were due to locoregional progression and that 40% to70% were due to distant metastasis (2, 3, 7, 9–11). In addition, several autopsy studies demonstrated that 20% to 28% of pancreatic cancer patients had no evidence of distant metastasis at the time of death (9, 11). Thus, it is necessary to improve the control of both distant metastasis and locoregional disease by use of combined systemic and local treatment (such as CRT) to achieve the improvement of survival in these patients. However, CRT is associated with

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CLINICAL INVESTIGATION **Bile Duct**

ROLE OF ADJUVANT CHEMORADIOTHERAPY FOR RESECTED EXTRAHEPATIC BILIARY TRACT CANCER

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Purpose: To evaluate the effect of adjuvant chemoradiotherapy (CRT) on locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) for patients with extrahepatic biliary tract cancer treated with curative resection.

Methods and Materials: The study involved 168 patients with extrahepatic biliary tract cancer undergoing curative resection between August 2001 and April 2009. Of the 168 patients, 115 received adjuvant CRT (CRT group) and 53 did not (no-CRT group). Gender, age, tumor size, histologic differentiation, pre- and postoperative carbohydrate antigen 19-9 level, resection margin, vascular invasion, perineural invasion, T stage, N stage, overall stage, and the use of adjuvant CRT were analyzed to identify the prognostic factors associated with LRC, DFS, and OS.

Results: For all patients, the 5-year LRC, DFS, and OS rate was 54.8%, 30.6%, and 33.9%, respectively. On univariate analysis, the 5-year LRC, DFS, and OS rates in the CRT group were significantly better than those in the no-CRT group (58.5% vs. 44.4%, $p = .007$; 32.1% vs. 26.1%, $p = .041$; 36.5% vs. 28.2%, $p = .049$, respectively). Multivariate analysis revealed that adjuvant CRT was a significant independent prognostic factor for LRC, DFS, and OS ($p < .05$).

Conclusion: Our results have suggested that adjuvant CRT helps achieve LRC and, consequently, improves DFS and OS in patients with extrahepatic biliary tract cancer.

Extrahepatic biliary tract cancer, Chemoradiotherapy, Survival.

INTRODUCTION

Extrahepatic biliary tract cancer (EHBTC) is a rare malignancy that arises from the epithelial cells of the biliary tract and has a tendency to extend longitudinally along the biliary tract or transversely into the adjacent tissues (1, 2). Patients with EHBTC have had poor overall survival (OS). The range of OS has been 2–3 months for patients receiving medical management alone, 6–12 months for patients undergoing palliative biliary bypass, and 12–24 months for patients undergoing resection (3, 4). Resection has been the only potentially curative treatment. However, even in patients undergoing curative resection, the prognosis has remained poor, with local failure rates related to morbidity and mortality of >50% in contemporary series (5–9). Given these poor outcomes, adjuvant therapy should be considered for these patients. However, although adjuvant therapy, such as chemoradiotherapy (CRT) or radiotherapy (RT), has been tried in patients with EHBTC after resection, the benefits of adjuvant therapy for those patients remains unclear (10–12). Moreover, because of the low incidence and complexity of the tumor (*i.e.*, the type and morbidity of the surgical procedure chosen and tumor resectability could be affected by tumor location), prospective studies of the different treatment modalities have been difficult to conduct and have rarely been accomplished. Thus, additional examination of the role of adjuvant therapy for patients with resected EHBTC is needed, even if as a retrospective study.

In the present study, we retrospectively analyzed our institutional outcomes for patients with resected EHBTC who had or had not undergone adjuvant CRT. We also evaluated the effect of adjuvant CRT on the long-term outcomes, such as locoregional control (LRC), disease-free survival (DFS), and overall survival (OS), in these patients.

METHODS AND MATERIALS

Patients

Between August 2001 and April 2009, 181 patients with EHBTC underwent curative resection at the National Cancer Center

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RADIATION ONCOLOGY

RESEARCH **Open Access**

Clinical outcomes of chemoradiotherapy for locally recurrent rectal cancer

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Abstract

Background: To assess the clinical outcome of chemoradiotherapy with or without surgery for locally recurrent rectal cancer (LRRC) and to find useful and significant prognostic factors for a clinical situation.

Methods: Between January 2001 and February 2009, 67 LRRC patients, who entered into concurrent chemoradiotherapy with or without surgery, were reviewed retrospectively. Of the 67 patients, 45 were treated with chemoradiotherapy plus surgery, and the remaining 22 were treated with chemoradiotherapy alone. The mean radiation doses (biologically equivalent dose in 2-Gy fractions) were 54.6 Gy and 66.5 Gy for the chemoradiotherapy with and without surgery groups, respectively.

Results: The median survival duration of all patients was 59 months. Five-year overall (OS), relapse-free (RFS), locoregional relapse-free (LRFS), and distant metastasis-free survival (DMFS) were 48.9%, 31.6%, 66.4%, and 40.6%, respectively. A multivariate analysis demonstrated that the presence of symptoms was an independent prognostic factor influencing OS, RFS, LRFS, and DMFS. No statistically significant difference was found in OS ($p = 0.181$), RFS ($p = 0.113$), LRFS ($p = 0.379$), or DMFS ($p = 0.335$) when comparing clinical outcomes between the chemoradiotherapy with and without surgery groups.

Conclusions: Chemoradiotherapy with or without surgery could be a potential option for an LRRC cure, and the symptoms related to LRRC were a significant prognostic factor predicting poor clinical outcome. The chemoradiotherapy scheme for LRRC patients should be adjusted to the possibility of resectability and risk of local failure to focus on local control.

Background

Recent advances in preoperative evaluation, treatment strategies and rectal cancer modalities have lead to better survival outcomes for patients with rectal cancer and a lower incidence of local recurrence [1,2]. Despite such improvements, 6-10% of patients with primary rectal cancer still experience intrapelvic local recurrence with or without distant metastasis [3-5]. These patients show a poor survival outcome with a nearly zero 5-year survival and 3-12 months of median survival when treated by only supportive care or palliative treatment [4]. Moreover, troublesome symptoms related to local recurrence reduce the quality of life during surviving periods. Recent studies have reported that radical surgery with microscopic curative resection presents a 48-60% long-term survival rate in patients surviving at 5 years [3,4,6-9]. These observations suggest that local control of LRRC is significantly associated with long-term survival and that the first goal of LRRC treatment should be local tumor control [5].

However, an aggressive approach with surgery alone also has severe weaknesses in that curative surgery is possible for only 20-30% of patients with locally recurrent rectal cancer (LRRC), because the intrapelvic space is too narrow to perform an R0 resection, and previous treatments, including surgery and radiotherapy, induce extensive fibrosis [3,4]. Moreover, high post-operative morbidities, of 30-60% [6-8], and the non-operable state of some patients should also be considered in the clinical situation. To compensate for the shortage of radical surgery, chemoradiotherapy (CRT) with adjuvant or curative intent has a definitive role in improving the

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CLINICAL INVESTIGATION **Lung**

THE EFFECT OF A CONTRAST AGENT ON PROTON BEAM RANGE IN RADIOTHERAPY PLANNING USING COMPUTED TOMOGRAPHY FOR PATIENTS WITH LOCOREGIONALLY ADVANCED LUNG CANCER

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Purpose: We evaluated the effect of a contrast agent (CA) on proton beam range in a treatment planning system (TPS) for patients with locoregionally advanced lung cancer.
Methods and Materials: Two sets of computed tomography (CT) images (with and without CA) were obtained from 20 patients with lung cancer. Because the increase in Hounsfield unit (ΔHU) value of the heart and great vessels due to the effect of CA is most prominent among thoracic structures, to evaluate the effect of CA on proton beam range in the TPS, we compared the calculated distal ranges in the plan with CA-enhanced CT with those with corrected CT, in which the HU values of the heart and great vessels in the CA-enhanced CT were replaced by average HU values obtained from the unenhanced CT.
Results: The mean ΔHU value and the longest length of the heart and great vessels within the proton beam path in the field that passed through these structures were 189 ± 29 HU (range, 110–250 HU) and 7.1 ± 1.1 cm (range, 2.6–11.2 cm), respectively. The mean distal range error in the TPS because of the presence of CA was 1.0 ± 0.7 cm (range, 0.2–2.6 cm).
Conclusion: If CA-enhanced CT images are used for radiotherapy planning using a proton beam for the treatment of lung cancer, our results suggest that the HU values of the heart and great vessels should be replaced by the average HU values of soft tissue to avoid discrepancies between planned and delivered doses.

Proton, Hounsfield unit, Contrast agent.

INTRODUCTION

Radiotherapy (RT) using a proton beam has led to marked advances in treatment, mainly because of its excellent dose distribution resulting from well-localized energy deposition at the end of the beam path, the so-called Bragg peak (1, 2). Because of a sharp distal fall-off of the Bragg peak in proton beams, the target volume can be delivered with high precision in three dimensions. The use of a high-precision proton beam requires a treatment planning system (TPS) of equal accuracy. However, there are various uncertainties in TPS, which can lead to discrepancies between the planned and delivered dose distributions. One of these potential sources is an iodine-containing contrast agent (CA) if CA-enhanced computed tomography (CT) images are used for RT planning, because the CA is present only during the planning process and not during the actual RT. In RT using X-rays, the use of a CA in a TPS is generally considered acceptable; the CA has a negligible effect because of a relatively low concentration in tissues and the shallow slope of the depth-dose distribution of high-energy X-rays (3–7). However, the range of a proton beam is determined by empiric correlation between stopping power in tissue and the value in Hounsfield units (HU) of CT images (8–11). Thus, the use of a CA is expected to lead to more significant errors in TPS using a proton beam compared with TPS using X-rays.

A previous study evaluated the effect of a CA on proton and heavy ion beam range (12). The results indicated that the increased HU values of soft tissue tumors and normal brain tissue that result from use of a CA led to an error of less than 2.5% in range when skull-base tumors were treated. In other words, the CA-induced increase in the HU value of tissues within the skull-base region was too small to significantly influence calculation of the heavy ion and proton beam ranges. Conceptually, a CA-induced range shift of a proton beam in a TPS is attributable to the increased extent

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Clinical Investigation

Phase 3 Trial of Postoperative Chemotherapy Alone Versus Chemoradiation Therapy in Stage III-IV Gastric Cancer Treated With R0 Gastrectomy and D2 Lymph Node Dissection

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Summary

The benefit of chemoradiation therapy in patients treated with R0 gastrectomy and D2 lymph node dissection remains controversial. We designed this study to compare chemotherapy alone with chemoradiation therapy in stage III-IV(M0) gastric cancer. Addition of radiation therapy to chemotherapy could improve the LRRFS in stage III gastric cancer treated with R0 gastrectomy and D2 lymph node dissection.

Purpose: To compare chemotherapy alone with chemoradiation therapy in stage III-IV(M0) gastric cancer treated with R0 gastrectomy and D2 lymph node dissection.
Methods and Materials: The chemotherapy arm received 5 cycles of fluorouracil and leucovorin (FL), and the chemoradiation therapy arm received 1 cycle of FL, then radiation therapy of 45 Gy concurrently with 2 cycles of FL, followed by 2 cycles of FL. Intent-to-treat analysis and per-protocol analyses were performed.
Results: Between May 6, 2002 and June 29, 2006, a total of 90 patients were enrolled. Forty-four were randomly assigned to the chemotherapy arm and 46 to the chemoradiation therapy arm. Treatment was completed as planned by 93.2% of patients in the chemotherapy arm and 87.0% in the chemoradiation therapy arm. Overall intent-to-treat analysis showed that addition of radiation therapy to chemotherapy significantly improved locoregional recurrence-free survival (LRRFS) but not disease-free survival. In subgroup analysis for stage III, chemoradiation therapy significantly prolonged the 5-year LRRFS and disease-free survival rates compared with chemotherapy (93.2% vs 66.8%, $P=.014$; 73.5% vs 54.6%, $P=.056$, respectively).
Conclusions: Addition of radiation therapy to chemotherapy could improve the LRRFS in stage III gastric cancer treated with R0 gastrectomy and D2 lymph node dissection.

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Curative Radiotherapy using Different Radiation Techniques for Isolated Lung Metastasis from Colorectal Cancer

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Running title: RT for lung metastasis of colorectal cancer

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Competing Interest

The authors have no conflicting interests to declare.

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Original Article

Stage-to-stage Comparison of Neoadjuvant Chemotherapy Versus Adjuvant Chemotherapy in Pathological Lymph Node Positive Breast Cancer Patients

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Objective: The purpose of this study was to investigate the prognostic implications of post-neoadjuvant chemotherapy on the survival outcomes of breast cancer patients with persistent positive axillary lymph nodes by performing a stage-to-stage comparison between neoadjuvant chemotherapy and initial surgery.
Methods: Retrospective analysis was performed on 813 breast cancer patients with positive axillary lymph node after surgery, who were treated between 2001 and 2006. Of these, 269 patients received neoadjuvant chemotherapy, and 544 patients were treated with surgery followed by adjuvant chemotherapy. The median follow-up time was 5.9 years.
Results: The 5-year disease-free survival rates for patients in the neoadjuvant chemotherapy and adjuvant chemotherapy groups were 73 and 88%, respectively ($P < 0.001$). The 5- and 9-year disease-free survival rates for ypStage II (82 and 76%) were significantly worse than those for pStage II (93 and 80%, $P = 0.002$), and the rates for ypStage III (64 and 50%) were worse than those for pStage III (74 and 66%, $P = 0.04$). The disease-free survival of ypStage II was similar to that of pStage III ($P = 0.16$). Similar results were seen when comparing distant metastasis-free survival rates. Using multivariate analyses, grade, age, hormonal receptor status, final pathological stage and neoadjuvant chemotherapy itself were found to be independent negative prognostic factors for disease-free survival.
Conclusions: Stage-to-stage comparison of pathologically node-positive patients revealed that the survival outcome at each ypStage after neoadjuvant chemotherapy was worse than that for the comparable pStage. These data may help to formulate more accurate prognoses for patients with residual positive nodes after neoadjuvant chemotherapy.

Key words: breast neoplasm – neoadjuvant treatment – disease-free survival

INTRODUCTION

Several clinical trials have demonstrated the comparable outcomes of neoadjuvant chemotherapy (NCT) and adjuvant chemotherapy (ACT) (1–4). Pathological complete response (pCR) or negative axillary lymph node (ALN) after NCT is associated with a favourable long-term outcome, whereas non-pCR patients are reported to have poorer outcomes (3,5–8). Published rates of pathological responses after NCT