



# **Karaciğer Tümörlerinde Stereotaktik Beden Radyoterapisi (SBRT)**

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- Stereotaktik Beden Radyoterapisi (SBRT) ablatif radyasyon dozlarının 1-5 fr'da uygulanması
- Karaciğer lezyonlarında SBRT akciğer kanserinde SBRT ile özdeş ancak daha kompleks
- Bu nedenle öncelikli olarak kliniklerde SBRT'ye akciğer ile başlamak daha uygun ve önerilmekte

- Radyasyona bađlı KC hasarı için
  - Tüm karaciđer dozu >30 Gy
  - Ancak çođu malignitede 30 Gy tedavi için yeterli deđil

- Primer KC tümörleri
  - Hepatoselüler karsinom (HCC)
  - Kolanjiokarsinom
  - Hepatoblastom
  - Anjiosarkom
  - Hemanjiyoepitelyoma

- **HCC**

- HCC
  - En sık hepatobilier malignite
  - KC parankimi kaynaklı
  - E / K = 3
  - 6. dekatta pik
  - Viral:
    - Asya ve Afrika'da Hepatit B, Avrupa, Japonya ve Amerika'da Hepatit C
  - Non-viral:
    - Alkolik siroz, metabolik hastalıklar (Wilson, aflatoksin maruziyeti)
  - Sıklıkla asemptomatik
    - Non spesifik semptomlar sık (kilo kaybı, sarılık, halsizlik, üst karın ağrısı, hepatomegali, asit)

- HCC
  - Görüntüleme ve laboratuvar testleri sonrası
    - Potansiyel rezektable ya da transplantasyon yapılabilir
    - Unrezeke
    - Medikal inoperable
    - Metastatik hastalık
  - Evreleme
    - AJCC, Barselona Klinik KC Kanseri evrelemesi, İtalyan KC Kanseri Programı, Japon evrelemesi

## CHILD-PUGH SCORE

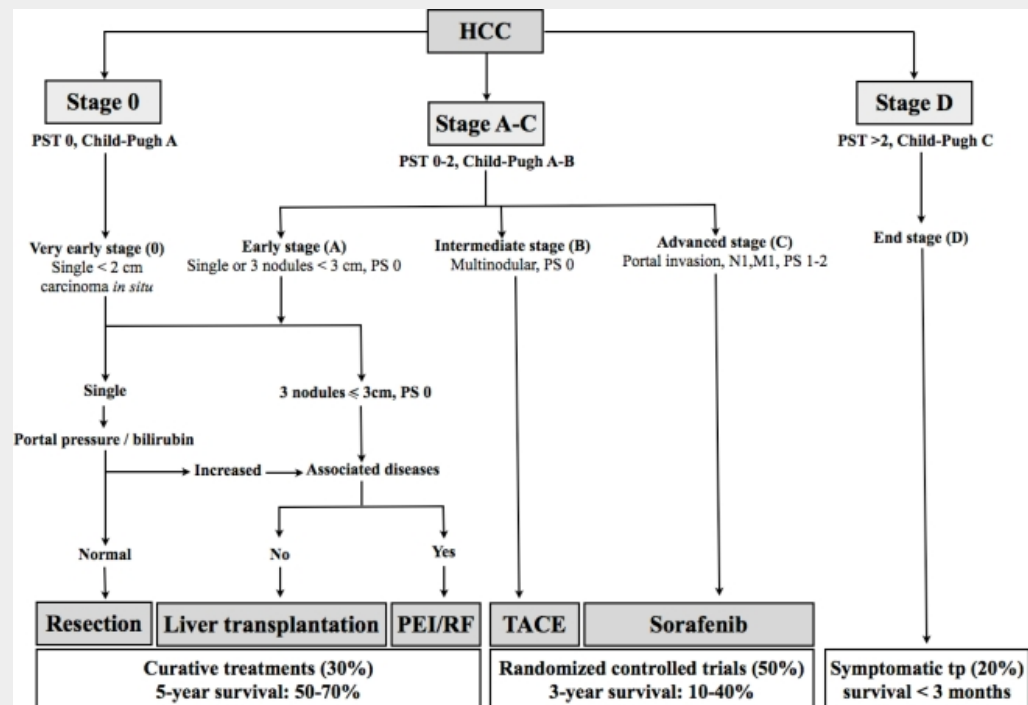
Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade) <sup>1</sup>	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time <sup>2</sup>			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Bilirubin (mg/dL)			
• For primary biliary cirrhosis	<2	2-3	>3
	<4	4-10	>10

Class A = 5-6 points; Class B = 7-9 points; Class C = 10-15 points.

Class A: Good operative risk

Class B: Moderate operative risk

Class C: Poor operative risk





- HCC (Tedavi edilmez ise median sağkalım 3-8 ay)
  - Tedavi
    - Mümkünse cerrahi
    - Mümkün değil ise Ablazyon ya da TACE ya da SBRT (Kategori 2B)
    - Performansı kötü, büyük damar komşuluğu, vasküler yolla ulaşılanın mümkün olmadığı durumlarda cerrahi/ablazyon/TACE mümkün değil
    - Transplant için UNOS kriterleri
      - <5 cm tek tm ya da 2-3 tm için < 3 cm, vasküler inv YOK, NOMO
    - Bilirubin >2 mg/dl ya da Child Pugh class C ise Y90'dan kaçının

- Prospektif faz I çalışma
  - Princess Margeret Hospital
  - 31 HCC, 10 intrahepatik kolanjiyel karsinom
  - Median 36 Gy / 6 fr (24-54 Gy)
  - Hastaların en az %60'ı daha önce 1 tedavi aldı
  - Medyan sağkalım 12 ay
- Mendez Romero ve ark. 8 hasta, 11 lezyon, HCC
  - 25-37,5 Gy, 3-5 fr
  - 1 yıllık GS %75

- Choi ve ark.
  - 23 hasta, 32 lezyon
  - 36 Gy / 3 fr
  - Medyan GS 11 ay
  - SBRT sonrası KC fonksiyonunda azalmaya neden olan faktörler incelendiğinde multivariye analizde tek faktör
    - 18 Gy alan normal KC volümünün >800 cc
- Kore çalışması
  - TACE sonrası nüks, 38 hasta, inoperabl HCC
  - Medyan tm volümü 40,5 cc (11-464), 33-57 Gy / 3-4 fr
  - Grad 2 toksisite <%3
  - 2 yıllık GS %61

- Cardenes ve ark.
  - Çok merkezli faz I doz artırımı çalışması
  - Child A ve B, medikal ve teknik inoperabl, 1-3 lezyon, <6 cm
  - 17 hasta, 25 lezyon,
  - 36 dan 48 Gy'e / 3 fr
  - Child A hastalarda toksisite YOK
  - Child B 2 hastada 42 Gy'de gr III KC toksisitesi ve 40Gy / 5 fr'a düşülmüş
  - Lokal başarısızlık YOK
  - 6 hasta KC transplantasyonuna gitmiş
  - 2 yıllık GS %60

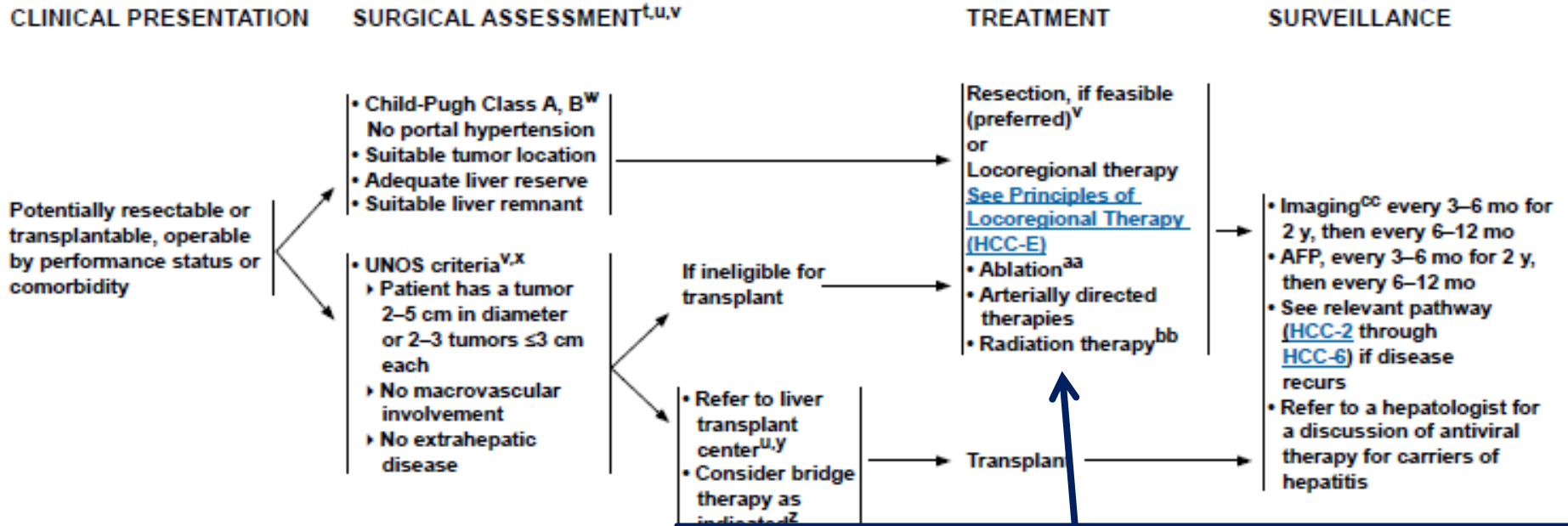
- İndiana Uni.
  - 34 Child A (3 x 14 Gy), 25 Child B (5 x 8 Gy) ve 1 Child C
  - Medyan takip süresi 27 ay
  - 2 yıllık lokal kontrol %90
  - 2 yıllık GS %67
  - SBRT sonrası 23 hasta KC transplatasyonuna gitti (Bridge to transplantation)
  - Tedavi sonrası ilk 3 ayda child evresinde progresyon hastaların %20'sinde görüldü

- En geniş kapsamlı çalışma, Bibault ve ark.
  - 75 hasta ve 96 lezyon, HCC
  - Child A 67 hasta
  - Child B 8 hasta
  - 40-45 / 3 fr, %80 RI
  - 1 ve 2 yıllık lokal kontrol %89,8
  - 1 ve 2 yıllık GS %78,5 ve %50,4
  - Grad 3 ve üzeri toksisite YOK
  - AFP yüksekliği ile lokal kontrol ters orantılı olarak bulundu
  - Child skoru 5 üzeri ise GS daha kötü

- Su ve ark.
  - Rezeksiyon vs SBRT karşılaştırması (propensity matching technique)
  - 1, 3 ve 5 yıllık GS açısından fark YOK
  - Toksikite benzer
  - SBRT uygulananlarda bulantı daha fazla

- HCC'de SBRT süreci
  - Hastanın klinik değerlendirmesi
  - Simülasyon
    - İmmobilizasyon ve tedavi pozisyonunda kılavuz görüntü (Kontrastlı KC MR)
  - RT'nin planlaması
  - RT'nin uygulanması
    - İmmobilizasyon, tedavi öncesi görüntüleme, fraksiyon esnasındaki hareketin kontrolü





Seçilmiş vakalarda SBRT'nin etkinliği ve güvenilirliği tek kollu çalışmalarda ve vaka serilerinde gösterilmiş

<sup>t</sup>Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.  
<sup>u</sup>Patients with Child-Pugh Class A liver function, who fit UNOS criteria ([www.unos.org](http://www.unos.org)) and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.  
<sup>v</sup>[See Principles of Surgery \(HCC-D\)](#).  
<sup>w</sup>In highly selected Child-Pugh Class B patients with limited resection.  
<sup>x</sup>Some patients beyond the Milan criteria can be considered for transplantation. Extended criteria/downstaging protocols are available at selected centers and through UNOS.  
<sup>y</sup>Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-700.  
<sup>z</sup>Many transplant centers consider bridge therapy for transplant candidates. ([See Discussion](#)).  
<sup>aa</sup>In well-selected patients with small, properly located tumors ablation should be considered as definitive treatment in the context of a multidisciplinary review. (Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 2012;57:794-802 and Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006, 243:321-328).  
<sup>bb</sup>Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. [See Principles of Locoregional Therapy \(HCC-E\)](#).  
<sup>cc</sup>Multiphasic abdominal/pelvic MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. [See Principles of Imaging \(HCC-A\)](#).

CLINICAL  
PRESENTATION

Unresectable  
• Inadequate  
hepatic  
reserve<sup>f</sup>  
• Tumor  
location

Evaluate whether  
patient is a candidate  
for transplant  
[See UNOS criteria  
under Surgical  
Assessment ([HCC-4](#))]<sup>v,y</sup>

Transplant  
candidate

- Refer to liver  
transplant  
center
- Consider bridge  
therapy as  
indicated<sup>z</sup>

Not a  
transplant  
candidate

TREATMENT

Transplant

Options:<sup>dd</sup>

- Locoregional therapy preferred<sup>ee,ff</sup>
  - Ablation
  - Arterially directed therapies
  - Radiation therapy<sup>bb</sup>
- Clinical trial
- Best supportive care
- Systemic therapy<sup>gg</sup>

Progression  
on or after  
systemic therapy<sup>gg</sup>

SURVEILLANCE

- Imaging<sup>cc</sup>  
every 3–6 mo for 2 y,  
then every 6–12 mo
- AFP, every 3–6 mo for  
2 y, then every 6–12 mo
- See relevant pathway  
([HCC-2](#) through [HCC-6](#))  
if disease recurs

Seçilmiş vakalarda SBRT'nin etkinliği ve güvenilirliği tek kollu çalışmalarda ve vaka serilerinde gösterilmiş

<sup>f</sup>See [Child-Pugh Score \(HCC-C\)](#) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

<sup>v</sup>See [Principles of Surgery \(HCC-D\)](#).

<sup>y</sup>Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-700.

<sup>z</sup>Many transplant centers consider bridge therapy for transplant candidates. ([See Discussion](#)).

<sup>bb</sup>Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. [See Principles of Locoregional Therapy \(HCC-E\)](#).

<sup>cc</sup>Multiphasic abdominal/pelvic MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. [See Principles of Imaging \(HCC-A\)](#).

<sup>dd</sup>Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.

<sup>ee</sup>See [Principles of Locoregional Therapy \(HCC-E\)](#).

<sup>ff</sup>Use of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive care. (Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164-1171) and (Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Lancet* 2002;359:1734-1739).

<sup>gg</sup>See [Principles of Systemic Therapy \(HCC-F\)](#).

## PRINCIPLES OF LOCOREGIONAL THERAPY

### II. Treatment Information (Continued)

#### C. Radiation Therapy:

##### • Treatment Modalities:

- ▶ EBRT is a treatment option for patients with unresectable disease, or for those who are medically inoperable due to comorbidity.
  - ▶ All tumors irrespective of the location may be amenable to radiation therapy (3D conformal radiation therapy, intensity-modulated radiation therapy [IMRT], or stereotactic body radiation therapy [SBRT]). Image-guided radiotherapy is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.
  - ▶ Hypofractionation with photons<sup>18</sup> or protons<sup>19,20</sup> is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended.
  - ▶ SBRT is an advanced technique of hypofractionated EBRT with photons that delivers large ablative doses of radiation.
  - ▶ There is growing evidence for the usefulness of SBRT in the management of patients with HCC.<sup>21,22</sup> SBRT can be considered as an alternative to the ablation/embolization techniques mentioned above or when these therapies have failed or are contraindicated.
  - ▶ SBRT (1–5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. The majority of data on radiation for HCC liver tumors arises from patients with Child-Pugh A liver disease; safety data are limited for patients with Child-Pugh B or poorer liver function. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence.<sup>23</sup> The safety of liver radiation for HCC in patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for Child-Pugh C patients.<sup>24,25</sup>
  - ▶ Proton beam therapy (PBT) may be appropriate in specific situations.<sup>26,27</sup>
  - ▶ Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain.
- Dosing:
- ▶ Dosing for SBRT is generally 30–50 Gy in 3–5 fractions, depending on the ability to meet normal organ constraints and underlying liver function. Other hypofractionated schedules >5 fractions may also be used if clinically indicated.

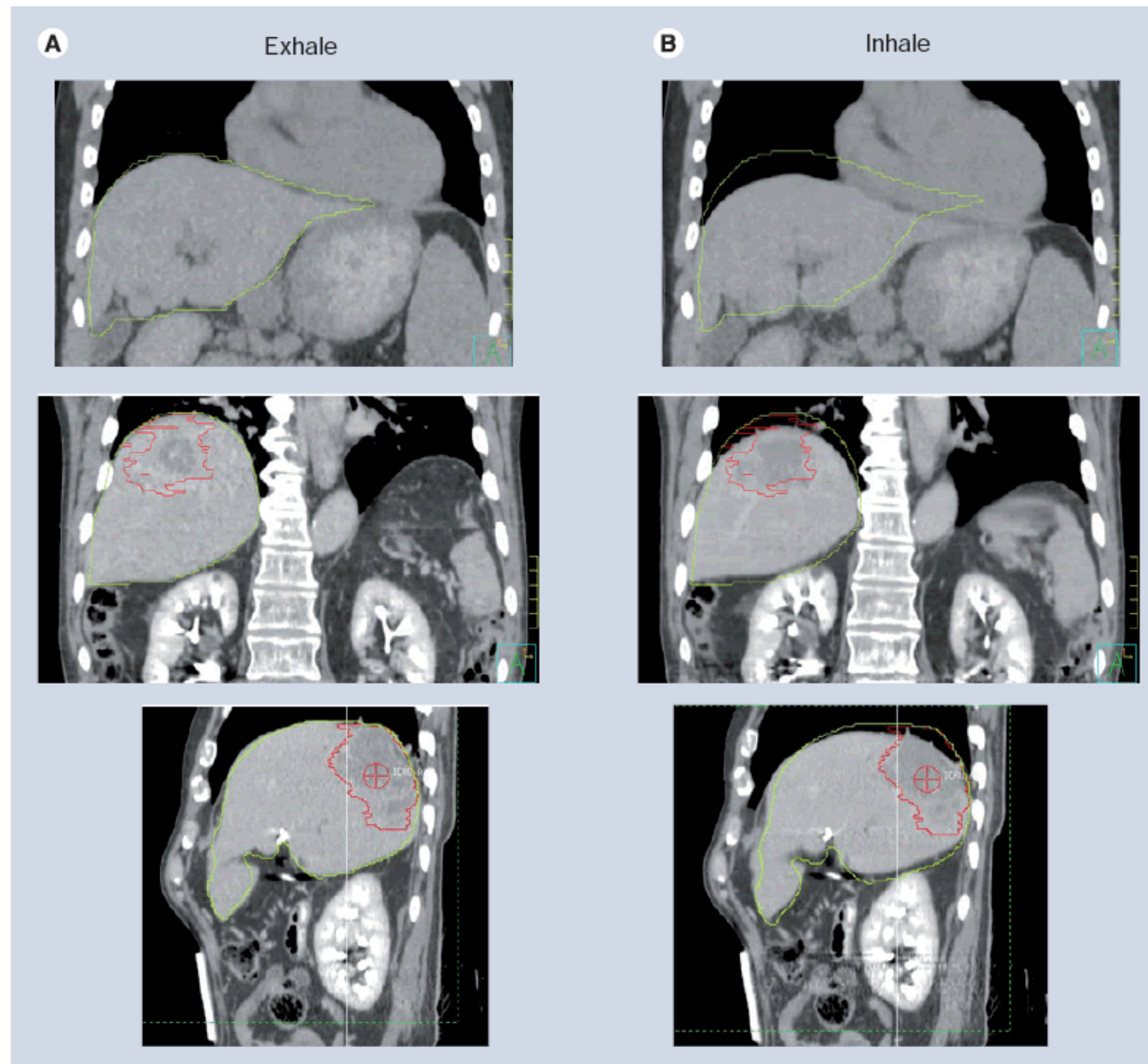
Sıklıkla 1-3 lezyon, yeterli KC kapasitesi varsa daha fazla ve daha büyük olabilir

Ekstrahepatik hastalık olmamalı

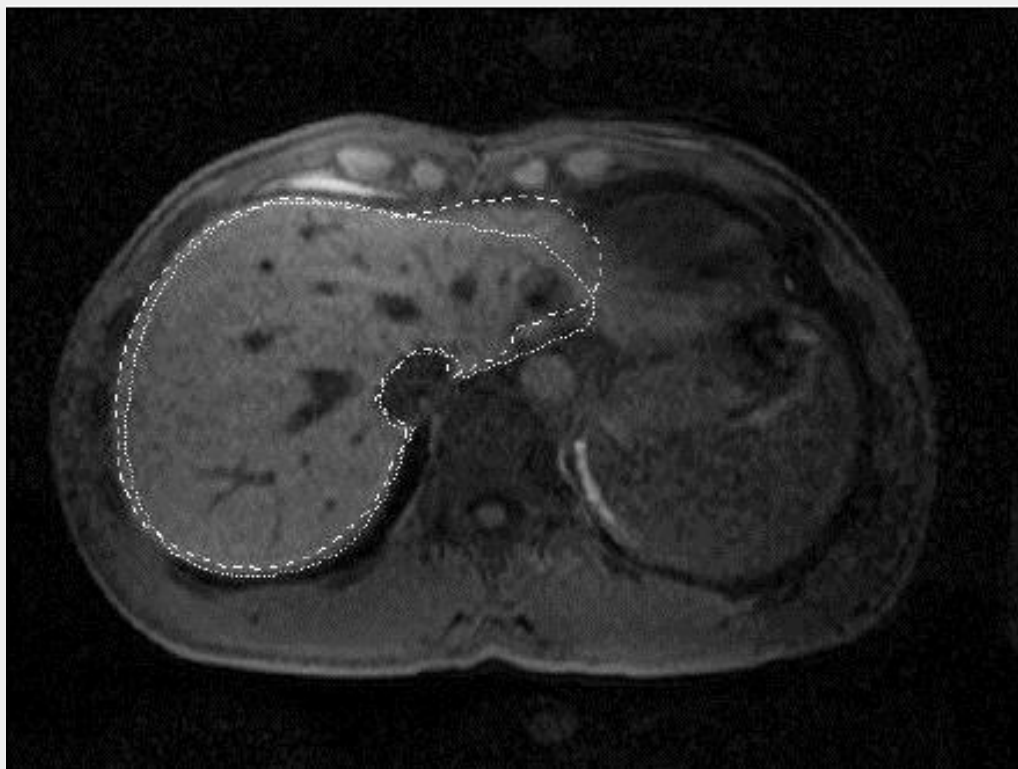
Tercihen Child A olmalı, Child B hastalarda doz modifikasyonu gerekli, Child C sadece çalışma bazlı

- Solunumsal hareketin kontrolü için
  - Hareketi değerlendirmek için 4D bilgisayarlı tomografi
  - Nefes tutma tekniği (*Breath hold*)
  - Abdominal kompresyon
  - Fiducial marker ile hedef takibi
  - Solunum takibi

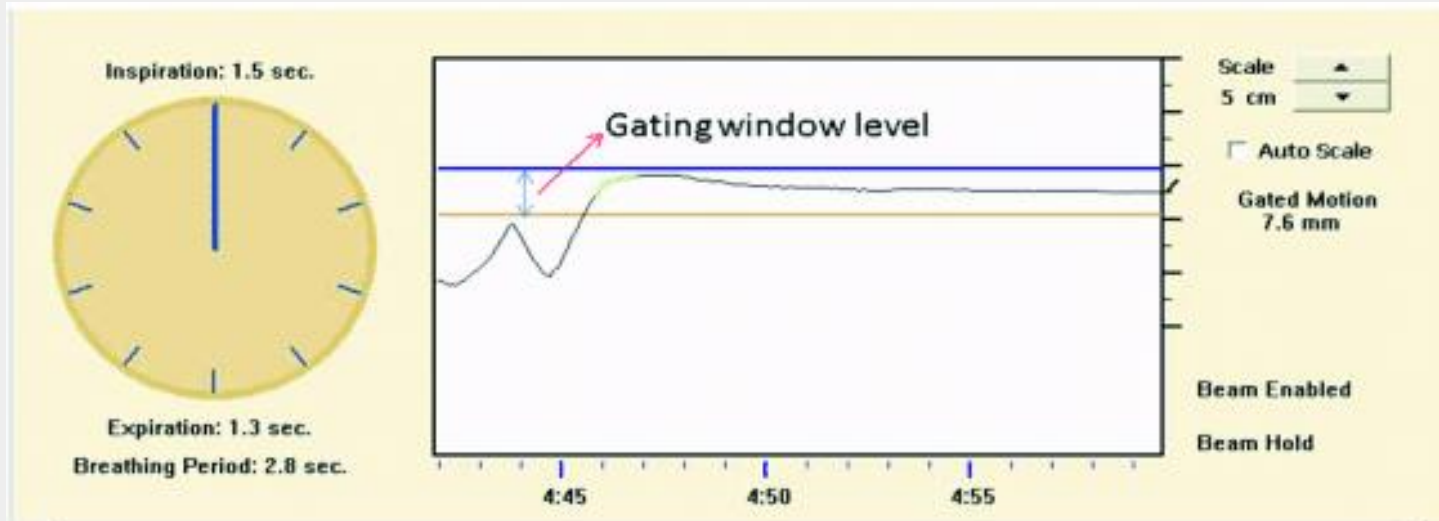
# 4D bilgisayarlı tomografi



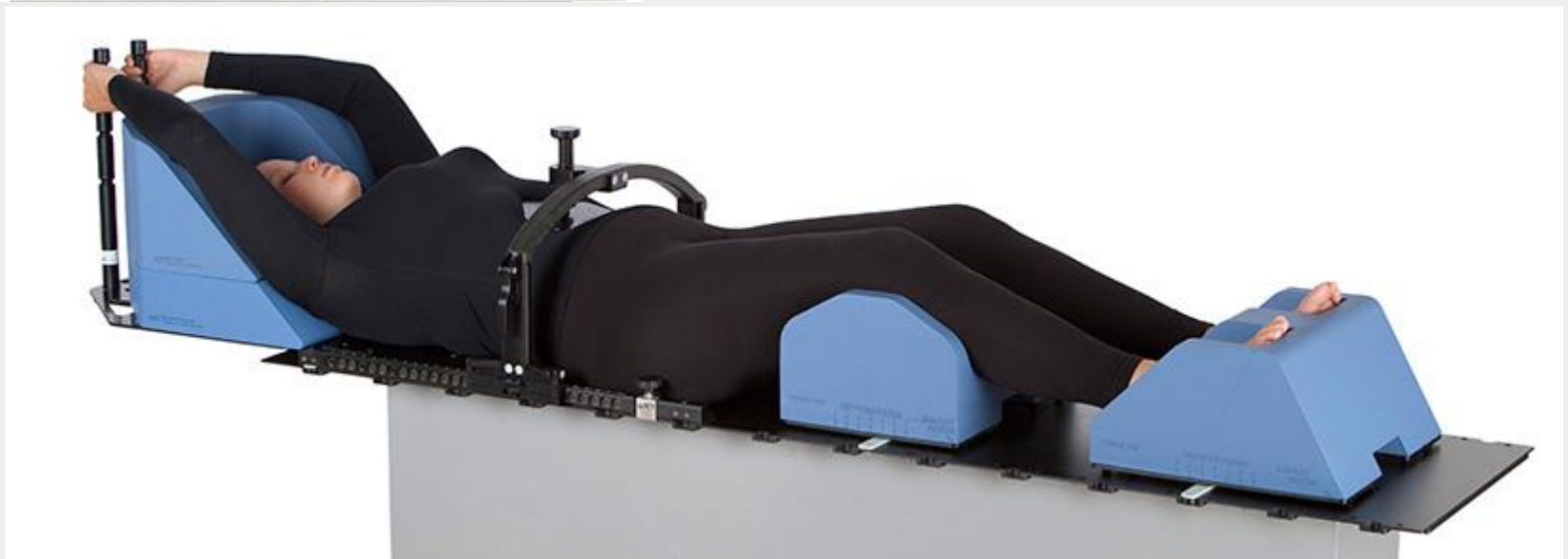
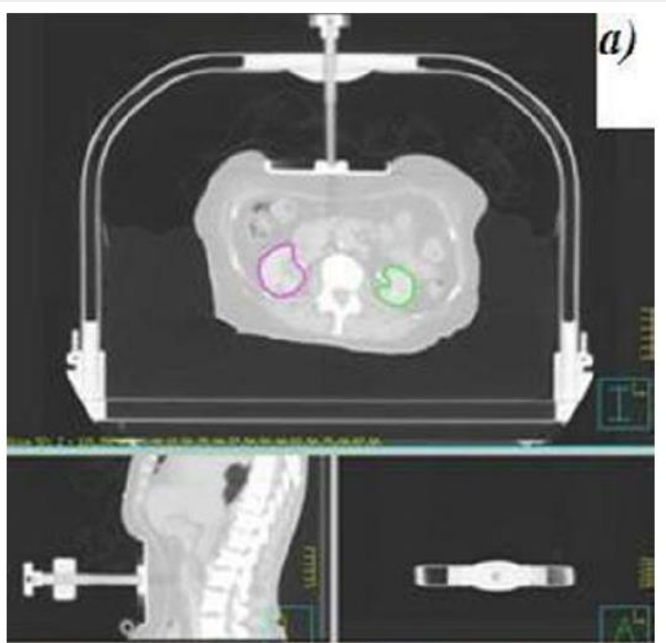
**Figure 3. Example of 4D CT, with exhale (A) and inhale phase 3D reconstructions (B).** The exhale liver (yellow) and liver tumor (red) contours are overlaid on the exhale and inhale reconstructions to demonstrate the change in position with breathing and evaluation of motion to define margins.



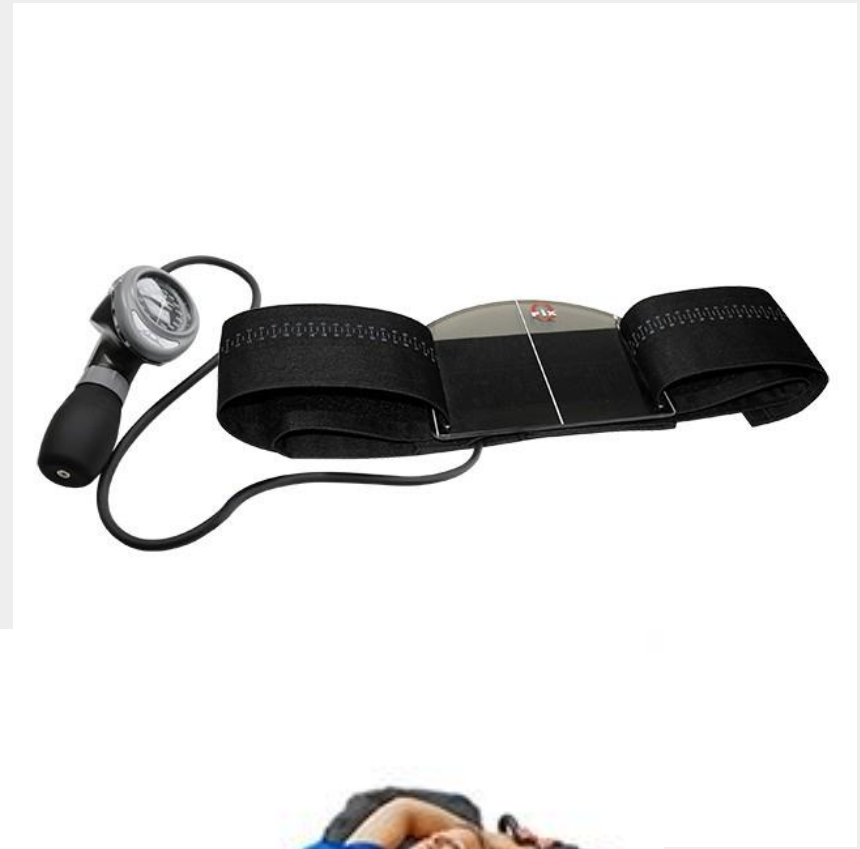
# Nefes tutma tekniği (*Breath hold*)



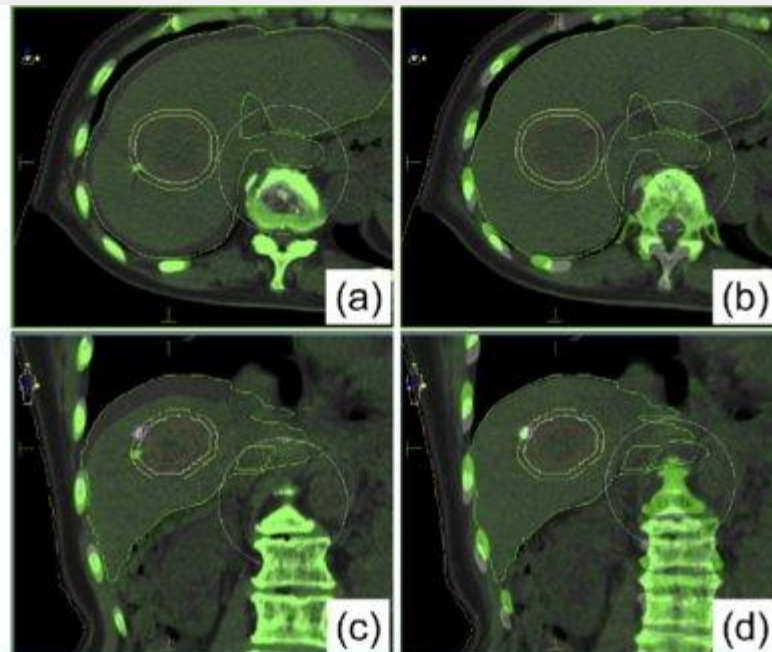
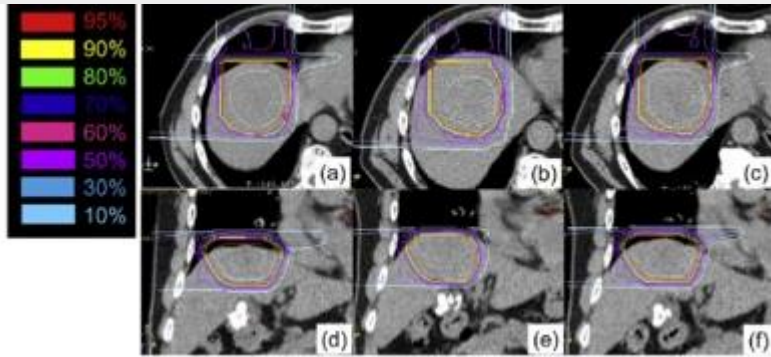
# Abdominal kompresyon





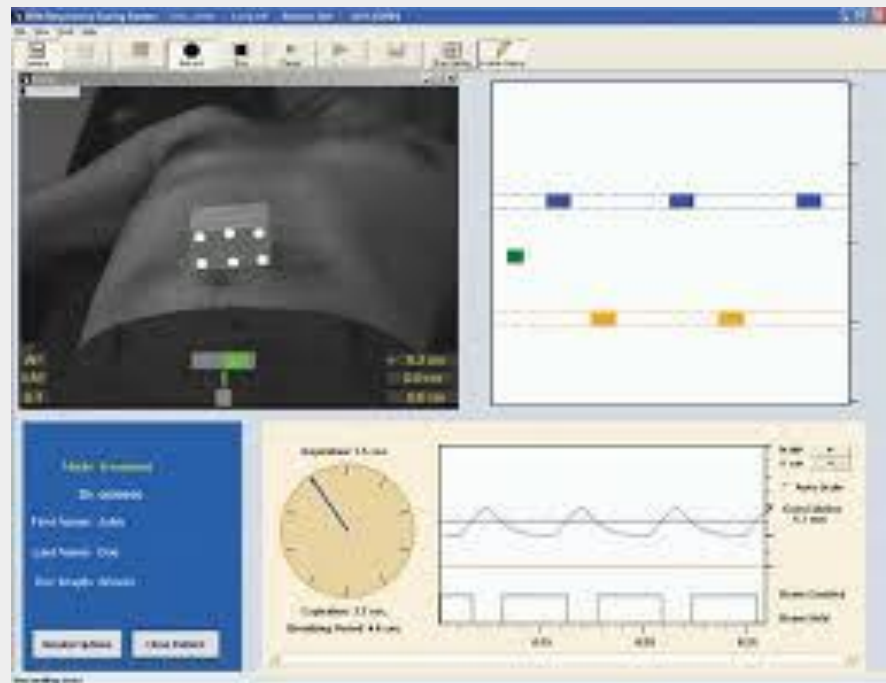


# Fiducial marker ile hedef takibi





Solunum takibi



- 4D Kontrastlı Planlama BT'si sonrası
  - GTV = görünür tm
  - ITV = solunumun tüm fazlarında görünür tm
  - PTV = ITV + 5-10 mm
- SBRT dozu
  - Fr başına 8 Gy'den PTV için 40 Gy, ITV için 50 Gy

# Plan

C1  
LiverSBRT

- BODY
- Bowel
- Bowel Avoid
- chestIN
- Chestwall
- Cord
- Cord+5mm
- CouchAnterior
- CouchSurface
- Duodenum
- HEART
- HeartAvoid
- iv
- Liver
- Liver Avoid
- LIVERINVOLVED
- Lt Kidney
- Pancreas
- PTV
- PTVplan
- PTVrig
- ring1
- Rt Kidney
- Spleen
- Stomach
- User Origin
- Reference Points
- Dose
- Fields

LiverSBRT - Treatment/Approach - Frontal - REGULAR

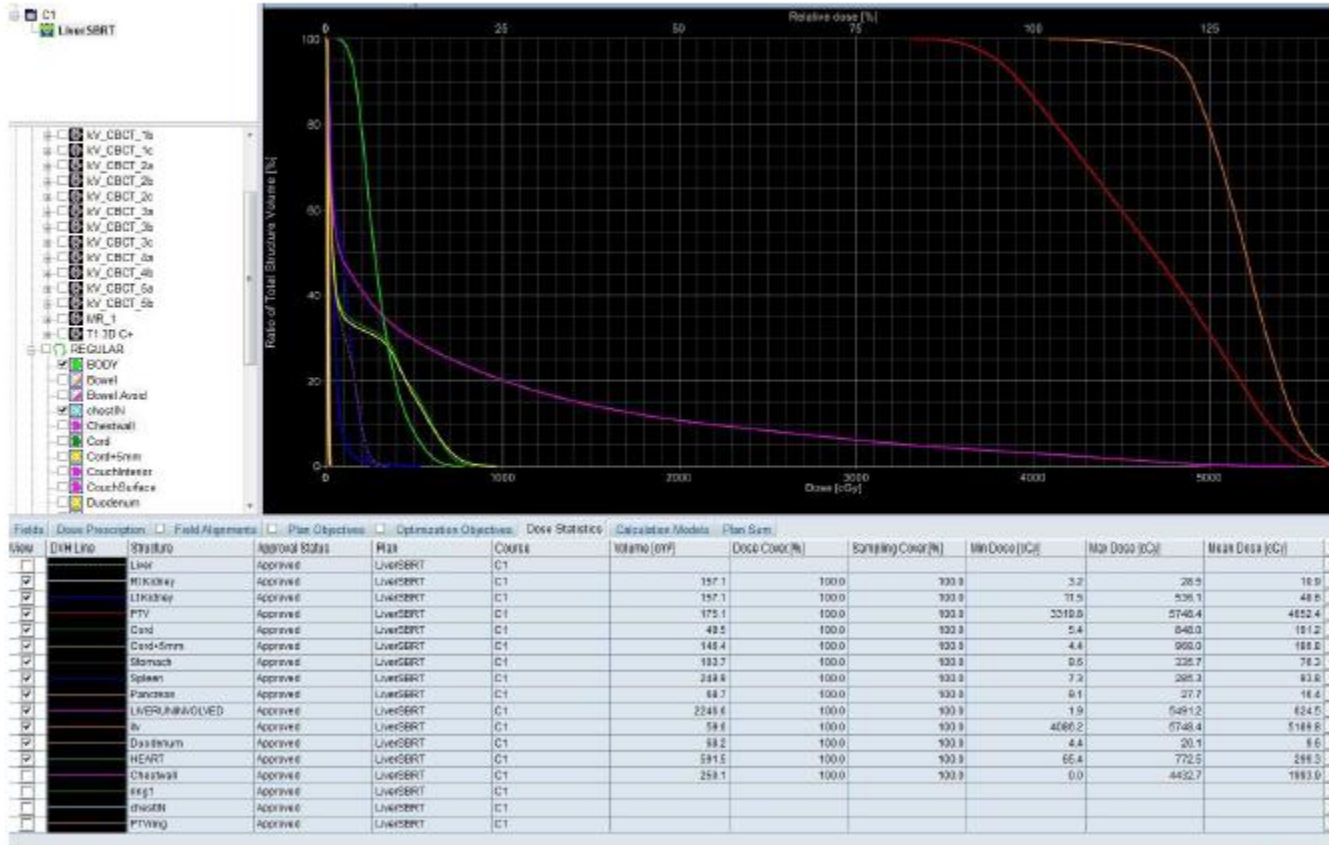
LiverSBRT - Treatment/Approach - Sagittal - REGULAR

LiverSBRT - Treatment/Approach - Coronal - REGULAR

LiverSBRT - Treatment/Approach - Axial - REGULAR

Group	Field ID	Technique	Machine/Energy	MLC	Field Weight	Scale	Gantry Rn (Deg)	Coll Rn (Med)	Couch Rn (Deg)	Wedge	Field X (cm)	X1 (cm)	X2 (cm)	Field Y (cm)	Y1 (cm)	Y2 (cm)	X [cm]	Y [cm]	Z [cm]	SSD (cm)	Wt	Ref D (Gy)	
<input checked="" type="checkbox"/>	CBCT	STATIC-I	TrueBeamSN1535 - 10kV-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	0.84	2.71	84.1			
<input checked="" type="checkbox"/>	1CW	SRS ARC-I	TrueBeamSN1535 - 10kV-FFF	VMAT	1.021	Varian IEC	181.8 CCW	0.0	10.0	0.0	None	8.4	+4.2	+4.2	9.5	+4.8	+4.8	-9.01	0.84	2.71	83.4	805	
<input checked="" type="checkbox"/>	CBCT Btan	STATIC-I	TrueBeamSN1535 - 10kV-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	0.84	2.71	84.1			
<input checked="" type="checkbox"/>	2CCW	SRS ARC-I	TrueBeamSN1535 - 10kV-FFF	VMAT	0.972	Varian IEC	0.0 CCW	181.0	350.0	0.0	None	8.7	+4.5	+4.2	9.5	+4.8	+4.8	-9.01	0.84	2.71	84.1	756	
<input checked="" type="checkbox"/>	AP SETUP	STATIC-I	TrueBeamSN1535 - 10kV-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	0.84	2.71	84.1			
<input checked="" type="checkbox"/>	RT LAT SETUP	STATIC-I	TrueBeamSN1535 - 10kV-FFF		0.000	Varian IEC	270.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	0.84	2.71	93.8			
<input checked="" type="checkbox"/>	AP OBI	STATIC-I	TrueBeamSN1535 - 10kV-FFF		0.000	Varian IEC	0.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	0.84	2.71	84.1			
<input checked="" type="checkbox"/>	RT LAT OBI	STATIC-I	TrueBeamSN1535 - 10kV-FFF		0.000	Varian IEC	270.0	0.0	0.0	None	10.0	+5.0	+5.0	10.0	+5.0	+5.0	-9.01	0.84	2.71	93.8			

# Plan



- Doz sınırlaması
  - Duodenum için
    - $\text{max} \leq 32 \text{ Gy}$
    - $< 5 \text{ cc} \leq 18 \text{ Gy}$
  - İnce Barsak için
    - $\text{Max} < 35 \text{ Gy}$
    - $< 5 \text{ cc} < 19,5 \text{ Gy}$
  - Sağlam KC için
    - $\text{KC-V21} > 700 \text{ cc}$
    - $\text{Mean} < 15 \text{ Gy}$

- **Kolanjiokarsinom**



- Kolanjiokarsinom
  - KC tümörlerinin %10'u ve sıklıkla >60 yaş
  - Safra kanalı epiteli kökenli
  - İntrahepatik / ekstrahepatik
  - >%90 Adenokarsinom
  - Nonspesifik semptomlar baskın (Ateş, kilo kaybı, karın ağrısı)

- Primer tedavi cerrahi (R0 rezeksiyon)
  - 5 yıllık GS %8-47
- R1 rezeksiyon sonrası
  - Rerezeksiyon
  - Kemoradyoterapi
  - Kemoterapi
  - Ablatif tedaviler

- Unrezeke tümörlerde
  - Kemoterapi
  - TACE
  - RF Ablazyon
  - Radyoterapi (Konvansiyonel, SBRT, brakiterapi, proton)
    - Prospektif Randomize çalışma YOK
  - Radyoembolizasyon

- Chen ve ark. 2010
  - 84 hasta (35 hastaya eksternal RT)
  - Medyan 50 Gy
  - Tam yanıt %9, Parsiyel yanıt %28,5
  - Medyan sağkalım 9,5 ay
- Shinohara ve ark. SEER verileri
  - Postoperatif ya da definitif RT ile GS daha yüksek

- 1 yıllık GS %36,1 - 73
- Tümör kontrolü %36-100
- Grad III-IV toksisite nadir
- Unrezeke hastalarda ağrı ve tıkanıklığın giderilmesinde başarılı

## PRINCIPLES OF RADIATION THERAPY

### I. General Principles

- Image-guided radiotherapy is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.

#### A. Adjuvant EBRT<sup>1,2</sup>

- ▶ Postoperative EBRT using conventional 3D conformal RT or IMRT is an option for resected extrahepatic cholangiocarcinoma and gallbladder cancer.<sup>3,4</sup> Target volumes should cover the draining regional lymph nodes to 45 Gy at 1.8 Gy/fraction and 50–60 Gy in 1.8–2 Gy/fraction to the tumor bed depending on margin positivity.

#### B. Unresectable

- ▶ All tumors irrespective of the location may be amenable to radiation therapy (3D conformal radiation therapy, IMRT, or SBRT).
- ▶ Conventionally fractionated radiotherapy with concurrent 5-fluorouracil-based chemotherapy to standard or high dose is acceptable for intrahepatic and extrahepatic tumors.
- ▶ Hypofractionation with photons<sup>5</sup> or protons<sup>6</sup> is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended.
- ▶ Dosing for SBRT for biliary tract tumors:
  - ◊ Is generally 30–50 Gy in 3–5 fractions, depending on the ability to meet normal organ constraints and underlying liver function.
  - ◊ Other hypofractionated schedules >5 fractions may also be used if clinically indicated.
  - ◊ For intrahepatic tumors, SBRT in 1–5 fractions is an acceptable option.<sup>5</sup>



Research Paper

# Stereotactic Body Radiotherapy (SBRT) for Intrahepatic and Hilar Cholangiocarcinoma

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2. Department of Surgery, Harvard Medical School, Boston, Massachusetts, USA
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**Background:** Unresectable intrahepatic and hilar cholangiocarcinomas carry a dismal prognosis. Systemic chemotherapy and conventional external beam radiation and brachytherapy have been used with limited success. We explored the use of stereotactic body radiotherapy (SBRT) for these patients.

**Methods:** Patients with unresectable intrahepatic or hilar cholangiocarcinoma or those with positive margins were included in this study. Systemic therapy was used at the discretion of the medical oncologist. The Cyberknife™ stereotactic body radiotherapy system used to treat these patients. Patients were treated with three daily fractions. Clinical and radiological follow-up were performed every three months.

**Results:** 34 patients (16 male and 18 female) with 42 lesions were included in this study. There were 32 unresectable tumors and two patients with resected tumors with positive margins. The median SBRT dose was 30Gy in three fractions. The median follow-up was 38 months (range 8-71 months). The actuarial local control rate was 79%. The median overall survival was 17 months and the median progression free survival was ten months. There were four Grade III toxicities (12%), including duodenal ulceration, cholangitis and liver abscess.

**Conclusions:** SBRT is an effective and reasonably safe local therapy option for unresectable intrahepatic or hilar cholangiocarcinoma.

**Unrezeke tabl, CyberKnife, 34 hasta, 30 Gy / 3 fr**

**Medyan takip 38 ay (8-71), lokal kontrol oranı %79, medyan OS 17 ay, medyan PFS 10 ay  
Grad 3 toksisire %12**

**Unrezeke hastalar için SBRT etkili ve güvenle uygulanabilir lokal tedavi seçeneği**



Scientific Article

# Stereotactic body radiotherapy (SBRT) for locally advanced extrahepatic and intrahepatic cholangiocarcinoma

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**Objectives:** We report single-institution clinical efficacy and safety outcomes for patients with unresectable locally advanced cholangiocarcinoma who were treated with stereotactic body radiation therapy (SBRT) and a subset of patients who received neoadjuvant SBRT and chemotherapy as part of an orthotopic liver transplantation (OLT) protocol.

**Methods and materials:** From October 2008 to June 2015, 31 consecutive patients with unresectable extrahepatic (n = 25) or intrahepatic (n = 6) cholangiocarcinoma were treated with SBRT and retrospectively analyzed. Four patients underwent liver transplantation, and 1 underwent resection. SBRT was delivered in 5 fractions with a median dose of 40 Gy. Toxicity was scored using the Common Terminology Criteria for Adverse Events Version 4.0. Overall survival (OS), time to progression, and local control were estimated using the Kaplan-Meier method.

**Results:** The median follow-up time was 11.5 months. The 1- and 2-year OS rates were 59% and 33%, respectively, with a median survival of 15.7 months. The 1- and 2-year freedom from progression was 67% and 34%, respectively. Median time to progression was 16.8 months. Nine patients had local failure. The actuarial 1- and 2-year local control rates were 78% and 47%, respectively. Among patients who also had OLT, the median OS was 31.3 months. Twenty-four patients (77%) experienced some form of acute grade 1-2 toxicity, most commonly fatigue or pain. Five patients (16%) experienced grade  $\geq 3$  toxicity.

**Conclusions:** SBRT is a promising option for patients with unresectable or recurrent cholangiocarcinoma either as a component of neoadjuvant therapy prior to OLT or as part of definitive therapy for patients who are unresectable and not eligible for transplantation.


Unrezektabl, 31 hasta, 40 Gy/5 fr,  
1 ve 2 yıllık OS %59, %33, Medyan 15,7 ay / OLT yapılanlarda 31,3 ay  
1 ve 2 yıllık PFS %67, %34, Medyan 16,8 ay  
1 ve 2 yıllık lokal kontrol oranı %78, %47  
9 lokal başarısızlık, gr 3 ve üzeri toksisite %16 (5 hasta)

RESEARCH ARTICLE

Open Access



# Stereotactic body radiotherapy (SBRT) for locally advanced intrahepatic and extrahepatic cholangiocarcinoma

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**Background:** To evaluate the role of ablative radiotherapy doses in the treatment of hilar or intrahepatic cholangiocarcinoma (CCC) using stereotactic body radiotherapy (SBRT).

**Methods:** Consecutive patients treated from 2007 to 2016 with CCC were evaluated. Local control and toxicities were assessed every 3 months according to the Response Evaluation Criteria In Solid Tumors (RECIST) and the Common Terminology Criteria for Adverse Events v4.0, respectively. Overall survival (OS), local control (LC) and progression free survival were calculated from SBRT.

**Results:** Thirty seven patients with 43 lesions were retrospectively evaluated. The median dose delivered was 45 Gy (range 25-66 Gy) in 3-12 fractions, corresponding to a median equivalent dose in 2 Gy fractions (EQD2<sub>10</sub>) of 56 (range 25-85) Gy. The median follow up was 24 months. The OS at 1 year was 56% with a median OS of 14 (95% CI: 7.8-20.2) months from start of SBRT and 22 (95% CI: 17.5-26.5) months from diagnosis. Eight lesions progressed locally. The local control rate (LC) at 1 year was 78%. The median progression free survival was 9 months (95% CI 2.8-15.2) 21 patients progressed in the liver but out of field and 15 progressed distantly. SBRT was well tolerated. Three patients (9%) developed a Grade III bleeding. Seven patients developed a cholangitis, one due to progression and the other because of a stent dysfunction 2-21 (median 8) months from SBRT.

**Conclusion:** In patients with locally advanced cholangiocarcinoma, SBRT is a local treatment option with an acceptable toxicity profile which warrants further investigation in prospective trials.

37 hasta/43 lezyon, 45 Gy (25-66) / 3-12 fr (EQD2 56 Gy (25-85 Gy)

Medyan takip 24 ay

1 yıllık OS %56, SBRT sonrası medyan 14 ay, tanı sonrası 22 ay

1 yıllık lokal kontrol %78, medyan PFS 9 ay

SBRT tolerasyonu iyi

- Sonuç olarak
  - Kolanjiokarsinom için SBRT
    - iyi tolere edilen
    - erken verilere bakıldığında lokal kontrol sonuçları olumlu bir tedavi

- **Metastatik hastalık**

- Karaciğerde görülen en sık malign lezyon metastaz (Metastatik / Primer = 20/1)
- Gastrointestinal sistem tümörlerinin %20'sinde tanı anında KC met +, sonrasında %20 hastada metastaz gelişmekte
- Kansere bağlı ölümlerde otopsi sonuçlarına göre KC'de metastaz varlığı %50

## SBRT: retrospective studies

STUDY	PATIENTS	LESIONS	RT DOSE	OUTCOME
<i>Blomgren et al, 1995</i>	14	17	7.7/45 Gy in 1/4 fr	<b>50% RR</b>
<i>Wulf et al, 2006</i>	39	51	30/37.5 Gy in 3 fr 26 Gy in 1fr	<b>1-year: 92%</b> <b>2-year: 66%</b>
<i>Katz et al, 2007</i>	69	174	30/55 Gy in 3-15 fr	<b>2-year: 57%</b>
<i>Van der Pool et al, 2010</i>	20 (only CRC)	31	30/37.5 Gy in 3 fr	<b>2-year: 74%</b>
<i>Vautravers-Dewas et al, 2011</i>	42 (CK)	62	40 Gy in 4 fr 45 Gy in 3 fr	<b>2-year: 86%</b>



## SBRT: prospective studies

STUDY	PATIENTS	LESIONS	RT DOSE	OUTCOME
<i>Herfarth et al, 2004</i> <i>Phase I/II</i>	35	51	14/26 Gy in 1 fr	<b>18 months:</b> <b>67%</b>
<i>Mendez et al, 2006</i> <i>Phase I/II</i>	17	34	30/37.5 Gy in 3 fr	<b>2-year: 86%</b>
<i>Hoyer et al, 2006</i> <i>Phase II</i>	44 (only CRC)	NA	45 Gy in 3 fr	<b>2-year: 79%</b>
<i>Lee et al, 2009</i> <i>Phase I/II</i>	68	140	28/60 Gy in 6 fr	<b>1-year: 71%</b>
<i>Rusthoven et al, 2009</i> <i>Phase I/II</i>	47	63	36/60 Gy In 3 fr	<b>2-year: 92%</b>
<i>Goodman et al, 2010</i> <i>Phase I</i>	19	33	18/30 Gy in 1 fr	<b>1-year: 77%</b>
<i>Rule et al, 2011</i> <i>Phase I</i>	26	35	30 Gy in 3fx 50 Gy in 5fx 60 Gy in 3fx	<b>2-year: 56%</b> <b>2-year: 89%</b> <b>2-year: 100%</b>

- **Local control: favorable**

- 1-year: 70% - 100% 2-years: 60% - 90%

- Results mainly dependent on tumor volume and RT dose

*Hoyer M et al, IJROBP, 2012*

- Toksisite
  - Grad 3 ve üzeri toksisite nadir
  - Tümör dışı normal KC hacmi 700 cc < 15 Gy

# SBRT: Italian phase I/II study

- *Prospective, phase I/II study of SBRT not amenable to surgery.*
  - KPS>70; adequate liver function
  - ≤ 3 hepatic lesions; maximum diameter 6 cm
- *Treatment procedures:*
  - 4DCT/gating procedures allowed
  - **Dose prescription: 75 Gy in 3 fractions with PTV covered by the 67% isodose**
- *Dose constraints:*
  - ≥ 700 cc of healthy liver should receive ≤ 15 Gy
  - Spinal chord Dmax: < 18 Gy
  - Kidneys V15: ≤ 35%
  - Stomach and duodenum Dmax: < 21 Gy
  - Rib cage V30: < 30 cc

# Stereotactic body radiation therapy for liver tumours using flattening filter free beam: dosimetric and technical considerations

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## Abstract

**Purpose:** To report the initial institute experience in terms of dosimetric and technical aspects in stereotactic body radiation therapy (SBRT) delivered using flattening filter free (FFF) beam in patients with liver lesions.

**Methods and Materials:** From October 2010 to September 2011, 55 consecutive patients with 73 primary or metastatic hepatic lesions were treated with SBRT on TrueBeam using FFF beam and RapidArc technique. Clinical target volume (CTV) was defined on multi-phase CT scans, PET/CT, MRI, and 4D-CT. Dose prescription was 75 Gy in 3 fractions to planning target volume (PTV). Constraints for organs at risk were: 700 cc of liver free from the 15 Gy isodose,  $D_{\max} < 21$  Gy for stomach and duodenum,  $D_{\max} < 30$  Gy for heart,  $D_{0.1 \text{ cc}} < 18$  Gy for spinal cord,  $V_{15 \text{ Gy}} < 35\%$  for kidneys. The dose was downscaled in cases of not full achievement of dose constraints. Daily cone beam CT (CBCT) was performed.

**Results:** Forty-three patients with a single lesion, nine with two lesions and three with three lesions were treated with this protocol. Target and organs at risk objectives were met for all patients. Mean delivery time was  $2.8 \pm 1.0$  min. Pre-treatment plan verification resulted in a Gamma Agreement Index of  $98.6 \pm 0.8\%$ . Mean on-line co-registration shift of the daily CBCT to the simulation CT were: -0.08, 0.05 and -0.02 cm with standard deviations of 0.33, 0.39 and 0.55 cm in, vertical, longitudinal and lateral directions respectively.

**Conclusions:** SBRT for liver targets delivered by means of FFF resulted to be feasible with short beam on time.

- Sonuç olarak hem primer hem de metastatik karaciğer tümörlerinde SBRT seçilmiş hastalarda güvenle uygulanabilir ve bu uygulamada teknolojik olarak gelişmiş LINAK cihazları oldukça yeterlidir.

# Varian TrueBeam



- 3 boyutlu konformal RT (3BKRT)
- Yoğunluk ayarlı RT (YART / IMRT)
- Görüntü kılavuzluğunda RT (GKRT / IGRT)
- RapidArc
- Stereotaktik beden radyoterapisi (SBRT) / Stereotaktik radyocerrahi (SRC)
- 6 boyutlu masa
- Yüksek çözünürlüklü (HD) MLC
- Solunum takibi / Fiducial takibi / Abdominal kompres
- 6 MV FFF (Düzleştirici filtresiz) foton ışını ve yüksek doz rate (hızı)



- Dinlediđiniz iđin teŖekkürler...