Food and Drug Administration-approved radiopharmaceutical for bone pain palliation. The therapeutic effect derives from the beta particles, which have an energy penetration range of up to 6–7 mm in soft tissues and 3–4 mm in bone [2]. Sr-89 has a half-life of 50.5 days, and decays to stable yttrium-89, emitting high-energy beta particles (E_{max}, 1.46 MeV) and 0.01 % of gamma-rays (910 keV). Administration poses no radiation risk to others, and patients can accordingly be treated on an outpatient basis. Studies of Sr-89 pharmacokinetics have demonstrated that plasma clearance is variable (1.6–11.6 l/day), with overall total-body retention of 20 % in a healthy population at 90 days after injection, particularly in the normal skeleton. Osteoblastic lesions show as much as five times greater radiopharmaceutical uptake and more prolonged retention than areas of normal bone in the same patient (lesion/normal bone ratio, 5:1) [3, 4].

Although the clinical profile of Sr-89 for prostate or breast cancer patients has been widely described [3, 5–9], little information is available concerning patients with other malignant diseases. Here, we conducted a retrospective analysis to clarify the clinical profile of Sr-89 in patients with multiple bone metastases arising from various other cancers.

Patients and methods

Patients

Entry criteria were a pathologically proven malignancy, clinical presence of multiple bone metastases detected by bone scintigraphy, and adequate organ function.

Patients eligible for external-beam radiotherapy (RT) or surgery were basically excluded from Sr-89 candidates.

Written informed consent for treatment was obtained from all patients before the initiation of treatment. This study was approved by the Institutional Review Board of National Cancer Center Hospital, Japan.

Pretreatment evaluation

All patients underwent a complete blood count and serum chemistry testing at entry. Patients who fulfilled any of the following criteria were ineligible: (1) white blood cell count less than 2,000/mm^3; (2) platelet count less than 75,000/mm^3; (3) hemoglobin less than 9 g/dl; and (4) serum creatinine greater than 2.0 mg/dl or creatinine clearance less than 30 ml/min. All patients underwent bone scintigraphy before treatment. Information about pain and analgesic effect was obtained by physician interview in accordance with standard NRS practice.

Protocol treatment

Sr-89 chloride (Metastron) was given by single intravenous infusion at 2 MBq/kg over 2 min followed by a 20-ml saline flush. Premedication was not routinely performed.

Follow-up, response evaluation, and toxicity

Patients visited the outpatient clinic for a complete blood test and interview every 2 weeks from the initiation of treatment until 2 months after treatment. Self-reported outcome measures were used as response index, including pain diary data on a 0–10 numeric rating scale (NRS) [10, 11]. Complete response (CR) was defined as a minimum NRS of 10 % or less than that at the initiation of treatment, partial response (PR) as a minimum of 50 % or less than that at the initiation of treatment, and no response (NR) as a minimum NRS of equal to or greater than that at the initiation of treatment.

Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Biweekly follow-up was continued until toxicities were easily manageable.

Statistical analysis

Survival curves were estimated using the Kaplan–Meier product-limits method with the log-rank test. Overall survival was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival time was censored at the last confirmation date if the patient was alive. Univariate analysis was conducted using the log-rank test.

Results

Patient characteristics

Fifty-four consecutive patients with painful bone metastases were treated with Sr-89 chloride at the National Cancer Center Hospital East between March 2009 and July 2011. All patients were reviewed. Patient characteristics are listed in Table 1. Twenty-six patients (48 %) had breast or prostate cancer. Twenty-six (48 %) had received chemotherapy in the 6 months before the initiation of treatment, among whom the median interval between the last chemotherapy and protocol treatment was 87 days (range, 0–164). Thirty-one patients had received prior palliative radiotherapy for bone metastases.

Of the patients, 23 (43 %) had received bisphosphonate therapy before Sr-89 administration, and all these patients

Table 1 Patient characteristics

	Total	Breast/prostate	Other
Number of patients	54	26	28
Age, median (range) (years)	64 (34–89)		
Gender, male/female	25/29	12/14	13/15
PS, 0–1/2/3	22/23/9	14/9/3	8/14/6
Primary site			
Breast		15	
Prostate		11	
Lung			8
Head and neck			6
Colorectal			6
Other			8

PS performance status

Table 2 Toxicity

	Grade (CTCAE ver. 4.0)		
	3	4	% 3/4
Leucopenia	0	1	1.8
Neutropenia	0	1	1.8
Anemia	5	1	11.1
Thrombocytopenia	2	2	7.4

CTCAE common terminology criteria for adverse events

continued to receive bisphosphonates during and after Sr-89 administration. Sixteen (70 %) of the breast/prostate cancer patients received bisphosphonate therapy, although only 7 patients (25 %) of patients with other cancers received therapy.

Toxicity

Thirteen (24 %) patients experienced a transient increase in pain, which was classified as a flare-up response. Profiling of other nonhematological toxicities was hampered by the frequent use of additional supportive interventions during and after protocol treatment, including morphine or other medications. Hematological toxicity is summarized in Table 2. Grade 3–4 anemia was observed in 6 patients, 3 of whom required blood transfusion within 2 months after protocol treatment. One patient developed disseminated intravascular coagulation (DIC), which might have been related to either Sr-89 administration or primary disease progression or to both.

Efficacy

Two patients were excluded from response evaluation because of sudden death unrelated to the use of Sr-89

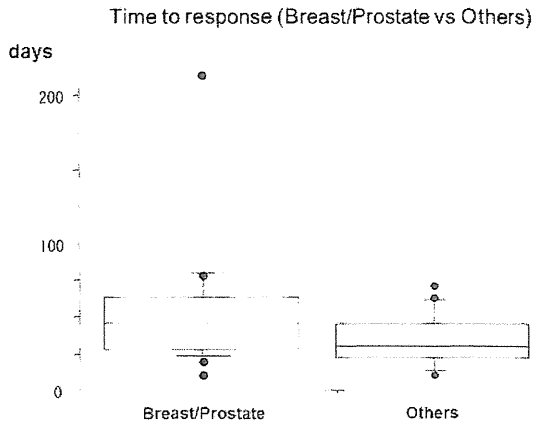

Fig. 1 Time to response (breast/prostate cancer vs. other). Time to response was calculated from the initiation of treatment to the day of pain relief (≥PR). Median time to response in breast/prostate cancer patients was 46 days (range, 13–217); that in other cancer patients was 31 days (range, 14–73). There was no significant difference between breast/prostate cancer patients and others

chloride. One patient with lung cancer died 7 days after Sr-89 administration. Hepatic failure caused by liver metastases was considered to be the main cause of death. Another patient with gastric cancer died 31 days after Sr-89 administration. At first visit after Sr-89, his performance status was 2. However, after the first visit, his condition was rapidly worsened by cachexia.

Overall response rate was 71.2 % and CR rate was 34.6 %. Median time to response was 36 days (range, 13–217 days). Median time to response in breast/prostate cancer patients was 46 days (range, 13–217), whereas that in other cancer patients was 31 days (range, 14–73) (Fig. 1).

Analgesic use at 2 months after treatment was decreased for only 11.5 % of patients. With a median follow-up period of 6.8 months, median survival time was 6.1 months and the 1-year overall survival rate was 28.0 %. Median survival time was significantly longer in patients with breast or prostate cancer than in those with other malignancies (Fig. 2).

Next treatment after Sr-89

After Sr-89 treatment, 9 patients received chemotherapy as a next treatment. The remaining 43 patients received best supportive care. Of those, 12 patients received palliative radiotherapy for bone metastases; median time from Sr-89 to next radiotherapy was 48 days (range, 13–252 days).

Predictive factors

Age, primary site (breast/prostate vs. others), history of chemotherapy, and onset of flare-up response were

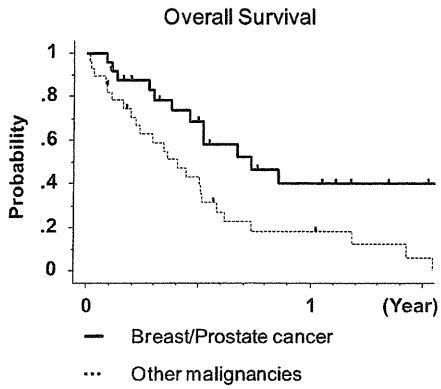

Fig. 2 Overall survival. Median survival time and 1-year survival rate were 8.0 months and 39.9 %, respectively, in patients with breast/prostate cancer, and 4.9 months and 17.9 % in those with other cancers. Overall survival was significantly longer in patients with breast/prostate cancer than in patients with other cancers ($p = 0.008$)

Table 3 Univariate analysis of predictive factors associated with response

	n	RR (%)	*P* value	HR (95 % CI)
Age (years)				1.01 (0.96–10.6)
Gender				
Male	23	73.9	0.70	0.78 (0.23–2.65)
Female	29	69		
Primary site				
Breast/prostate	26	72	0.76	1.21 (0.36–4.02)
Other	26	68.2		
Prior chemotherapy				
Yes	25	53.8	0.90	0.92 (0.28–3.07)
No	27	76.9		
Flare-up response				
Yes	13	53.8	0.12	2.86 (0.76–10.7)
No	39	76.9		

RR reponse rate, *HR* hazard ratio, *CI* confidence interval

investigated in univariate analysis (Table 3), but no significant predictive factor was identified.

Discussion

The clinical profile obtained in this study suggests that Sr-89 chloride may be of benefit in the treatment of painful bone metastases, not only in patients with breast and prostate cancer but also in those with various other malignancies.

Previous studies have identified hematological toxicity as one of the main side effects of Sr-89 chloride [6, 12, 13]. Hematological toxicities were present in the present study also but were of acceptable severity, albeit that the frequency of anemia was slightly higher than in previous reports. Further, the incidence of flare-up response was higher than with radiotherapy. Previous reports have shown similar results [6, 12], which appears to support the hypothesis that the incidence of flare-up response increases with increasing volume of bone metastases.

Among other findings, overall response rate was 71.2 % and CR rate was 34.6 %. Overall response rate was 69.2 % in breast and prostate cancer and 73.1 % in other cancers. These results showed that Sr-89 chloride had definite benefit in patients with painful bone metastases.

Our present results are of particular clinical valuable given the relative paucity of information about the clinical profile of Sr-89 chloride in cancers other than breast and prostate.

In this study, we used self-reported outcome measures as response index, including pain diary data on a 0–10 numeric rating scale (NRS). However, analgesic use was decreased for only 11.5 % of all patients at 2 months after treatment, and considerable discrepancy was seen between the results calculated by the diary and interview response indexes.

In clinical practice, analgesic use is seldom decreased even when the patient reports a decrease in bone pain. There are two major reasons for this: first, analgesics may also be required for other pain; and second, a decrease in analgesic use carries the risk that pain will recur. The recurrence of pain is a fatal outcome, particularly in patients receiving best supportive care. For these reasons, because a change in the amount of analgesics used does not reflect the response to Sr-89 chloride, we consider that this variable should not used as an index in clinical practice.

The predictive factors of response to Sr-89 are still controversial. Some investigators have found a better response in patients with good condition, and a poorer response with far-advanced metastatic disease [9, 14–16]. On the other hand, in some reports no significant difference was seen in patient background between responders and non-responders [17, 18].

In the present study, age, primary site (breast/prostate vs. other), history of chemotherapy, and onset of flare-up response were investigated in univariate analysis, but no significant predictive factor was identified.

The primary site of cancer and treatment history had no impact on the efficacy of Sr-89 chloride in univariate analysis, suggesting that Sr-89 chloride can be considered regardless of the primary site and treatment history.

Two major limitations of this study warrant mention. First, pain-free survival could not be evaluated because of the difficulty in conducting detailed and frequent interviews in patients receiving best supportive care. Second, the small scale and retrospective design of the study meant

that significant predictive factors of efficacy could not be adequately investigated.

Nevertheless, we consider that these results will be valuable for clinicians concerned with the difficult issue of bone pain control, particularly in view of the paucity of other data on this agent.

Conclusion

Sr-89 chloride may useful in the treatment of bone metastasis pain in patients with various malignancies, as it is in those with breast and prostate cancer.

Acknowledgments This study was supported by a Ministry of Education, Culture, Sports, Science and Technology scientific research grant.

Conflict of interest We have no conflict of interest.

Ethical standard In the present study, written informed consent for treatment was obtained from all patients before the initiation of treatment. This study was approved in Institutional Review Board of National Cancer Center Hospital, Japan.

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鼻副鼻腔悪性腫瘍に対する陽子線治療

全田貞幹 秋元哲夫

要 旨

陽子線治療は，水素の原子核を加速したもので放射線治療の一種である。陽子線は体内に入っても表面近くではエネルギーを放出せず，停止する直前にエネルギーを放出して大きな線量を組織に与える性質（ブラッグ・ピーク）があり，病巣の深さや大きさに合わせてこのピークの深さや幅を拡げることにより精密な治療を実現できる。特に視神経や脳などの重要臓器が近接する鼻副鼻腔領域ではこの特性を最大限に生かすことが可能である。

当院ではこれまで鼻・副鼻腔腫瘍に対する陽子線治療の成績を組織型別，および進行度別（T4もしくはKadish C）で発表してきた。

嗅神経芽細胞腫では5年生存率93%，悪性黒色腫においても3年生存率58.0%，頭蓋内浸潤を伴う悪性腫瘍に対する治療成績も3年生存率59.3%と，他のモダリティーに対して遜色ないと考えられる。

一方晩期毒性に関する検討では1999年から2008年に当院で陽子線治療を行った鼻副鼻腔腫瘍の患者で1年以上の経過をfollowしている患者91名を対象に追跡を行ったところ追跡期間中央値57.5ヶ月（12.4～162.7）で，grade 3，4の毒性出現率はそれぞれ14.4%，6.6%であった。grade 2以上の毒性が発生するまでの期間は39.2ヶ月であった。視力低下grade 4を5例確認したが3例は4年以上経過してから発症していた。

毒性に関しては3年以上経過してから発症する例が多く，観察期間が短いと過小評価してしまう危険がある。既報や他のモダリティーとの比較をおこなう場合には観察期間を揃える必要があると考えられた。

今後新規治療の有用性を示すには自治療の特性に加え競合治療との比較検討が必須と考える。施設が限られランダム化試験が難しい背景を考慮し，質の高い多施設共同のコホート研究をはじめ各々の施設の協力関係を築くことが求められるだろう。

キーワード：鼻腔腫瘍，陽子線治療，晩期毒性

Proton beam therapy for nasal cavity and/or paranasal malignancies:

Sadamoto Zenda and Tetsuo Akimoto
Department of Radiation Oncology, National Cancer Center Hospital East

Summary

Proton beams are characterized by their rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth, and delivery. These physical characteristics give proton beam therapy (PBT) a better dose distribution than X-ray irradiation, and PBT is now deemed a feasible and effective treatment modality that provides curative high-dose irradiation to the tumor volume without increasing normal tissue toxicity.

There are several published data about the outcomes of proton beam therapy for head and neck cancer from our institution. On the other hand, 91 patients who satisfied both criteria, definitive or postoperative PBT (> 50GyE) from January 1999 through December 2008, and more than 1 year follow-up, were traced to check the late toxicity. The median observation period was 57.5 months (range 12.4 ～ 162.7), and the median time to onset of Grade 2 or greater late toxicity except cataract was 39.2 months (range 2.7 ～ 99.8 months). Grade 4 visual loss occurred in 5 patients.

We consider that a relatively short observation period will result in the underestimation of late toxicity.

In the present study, we found many events which would not usually be encountered without long-term follow-up, and an adequate understanding of the toxicity profile of PBT in these patients thus requires long-term follow-up.

Key words：Proton beam therapy, Nasal cavity, Late toxicity

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国立がん研究センター東病院粒子線医学開発分野
全田 貞幹

陽子線治療の特徴

陽子は水素の原子核で，それを加速したものを治療応用したものが陽子線治療である。

陽子線治療は，エネルギーを粒子が停止する直前に放出するブラッグピークという性質を有しており[1]，それをさらに腫瘍の位置や大きさに調整することのできる拡大ブラッグピークを利用して，照射したい場所のみに線量を投与し腫瘍に近接する重要臓器を遮蔽することが理論上ほかのモダリティーより容易に達成することができる。陽子線の相対的生物学効果比（RBE; Relative Biological Effect）は1.1とほぼX線やガンマ線と同じであり，同じ物理線量の陽子線を照射した時の生物への効果は臨床的に同程度で，多くの共通の性質を持っている。つまり，陽子線照射の治療効果や，副作用を考慮する場合に，広く行われているX線やガンマ線による照射の経験やデータを，そのまま生かすことができる利点がある。現在の技術では実臨床において，いびつな形状や広い範囲に均一に照射することが難しくなっており予防照射を必要とする領域に対して陽子線治療は不向きと言える。

上記の特徴を考慮すると陽子線治療が最適な場合は

1. 腫瘍と正常重要臓器が近接しており通常の放射線治療では対処が困難。
2. 転移の少ない腫瘍で局所治療の比重が高い。
3. 手術治療を行うことで患者さんに大きな不利益が生じる可能性がある。

これら3つの条件は揃うときと考えることができる。

そのひとつが鼻副鼻腔，頭蓋底腫瘍である。

鼻副鼻腔悪性腫瘍に対する陽子線治療の治療成績

当院ではこれまで鼻・副鼻腔腫瘍に対する陽子線治療の成績を組織型別，および進行度別（T4もしくはKadish C）で発表してきた。

嗅神経芽細胞腫では5年生存率93%，悪性黒色腫においても3年生存率58.0%，頭蓋内浸潤を伴う悪性腫瘍に対する治療成績も3年生存率59.3%と，他のモダリティーに対して遜色ないと考えられる（表1）。鼻腔腫瘍は腫瘍の反応が他の疾患に比べて非常に遅く，治療後6ヶ月以上経って形態が残存しているが，PET-CTなどの機能診断では陰性となるケースがよくある。当院でも長期追跡の結果4年後にやっと消失を確認した嗅神経芽細胞腫の例を経験しており，陽子線治療の効果では一般的なresponse rateよりも1年腫瘍制御率のほうがよりよいサロゲートマーカーになりうると考える[2]。

鼻副鼻腔悪性腫瘍に対する陽子線治療の長期追跡による晩期毒性について

冒頭で陽子線の相対的生物学効果比（RBE; Relative Biological Effect）は1.1とほぼX線やガンマ線と同じであり，X線やガンマ線による照射の経験やデータを，そのまま生かすことができる利点がある，と触れたがブラッグピークの性質を利用することで晩期合併症の頻度は著しく改善することが理論的に可能と考えられている。しかしながら長期の成績に言及した論文は数少ない。

今回我々は1999年から2008年までに当院で陽子線治療を行った頭頸部がん患者の中で以下の条件を満たす91例について追跡調査を行った。

1. 1年以上生存している。
2. 陽子線治療後1年以降に国立がん研究センター東病院で診療を受けている。

患者背景を（表2）に示す。

半数以上がT4であり，もっとも多い原発部位は鼻腔であった。

結果は全観察期間の中央値が59.7ヶ月で致命的な晩期毒性（CTCAEver.3.0でGr.4）は6例（6.6%）に見られ，そのうち5例が失明であった。Gr.2以上の晩期毒性が発生するまでの期間の中央値は39.7ヶ月（範囲：3.7-115）であり，5年以上経過して失明に至った症例を2例経験した，詳細を表3に示す。これらの結果から，追跡が長期であればあるほどイベント数は増加し最低3年の追駅がなければ毒性の半分も拾い出すことは難しいということがわかった。

結果の解釈についてだが，諸家の報告との比較が困難であることには2つの理由がある。

①晩期毒性評価する指標が各施設で統一されていない。

②追跡期間に差があり，短いものは晩期毒性を過小評価している可能性がある。

表1　当院における鼻副鼻腔腫瘍の治療成績

著者	発表年	対象	治療成績	
西村ら[6]	2007	嗅神経芽細胞腫	5年生存率	93%
全田ら[7]	2011	悪性黒色腫	3年生存率	59.30%
全田ら[2]	2011	頭蓋底腫瘍	3年生存率	58.00%

表2　晩期毒性追跡91例の患者背景

年齢（歳）		57（17～84）
性別	男/女	53/38
原発巣	鼻腔	63
	副鼻腔	26
	その他	2
T stage	1（Kadish A）	4
	2（Kadish B）	17
	3	8
	4（Kadish C）	55
	再発	7
治療スケジュール	65GyE/26fr	62
	60GyE/15fr	17
	＞65GyE	10
	50-60GyE	2

表 3　陽子線治療後に失明をきたした症例のサマリー

Stage	治療レジメン	発症までの期間	現在の状態
T4	65GyE/26fr	6年6ヶ月	10年5ヶ月無病生存
Kadish A	65GyE/26fr	6年2ヶ月	7年3ヶ月無病生存
T4	65GyE/26fr	4年2ヶ月	5年2ヶ月無病生存
T4	60GyE/15fr	4年2ヶ月	4年6ヶ月無病生存
T4	60GyE/15fr	1年5ヶ月	4年7ヶ月他病死亡

①に関しては近年国内にも粒子線施設が複数新設され，多施設共同研究の余地が出てきたと考えるため各施設間で評価方法を統一し，前向き観察研究を行うことで非常に有用な結果が得られるのではと期待している。

②に関しては粒子線治療が安全であるという実験データのバイアスもあり初期に出た未熟な短期成績が実験データを裏付けるものであるとして公表されるケースが散見される。

Schulzら[3]は，頭蓋底腫瘍に対する放射線治療の晩期毒性（Gr.3以上）の発生頻度を1.3%と報告しているがその観察期間は2年未満であった。またDebusら[4]は髄膜腫に対する放射線治療で発生する晩期毒性の発生頻度は2.1%と報告しており，その観察期間中央値は35ヶ月であった。一方Leeら[5]は頭蓋底腫瘍に対する外照射の晩期毒性が34.6%発生すると報告しておりその観察期間中央値は56ヶ月であった。このように追跡期間が長くなると晩期毒性のデータはより真実に近づき数値は悪い方に傾くため，Up-dated resultとして晩期毒性のデータを下方修正する施設は少ない。

今回我々は長期観察することで既存のpublished dataから一部修正を行っている。

今後粒子線治療が外科や腫瘍内科，他分野の研究者に広く認知されるためには良いデータも悪いデータもすべて公表し世間での評価を受けることができる体制づくりが必要であると考える。

結　語

鼻副鼻腔腫瘍に対する陽子線治療の効果と安全性および今後の粒子線治療の課題について述べた。今後新規治療の有用性を示すには自治療の特性に加え競合治療との比較検討が必須と考える。

施設が限られランダム化試験が難しい背景を考慮し，質の高い多施設共同のコホート研究をはじめ各々の施設の協力関係を築くことが求められるだろう。

著者のCOI：全田　貞幹
日本化薬株式会社：講演料
メルク・セローノ社：講演料
ブリストル・マイヤーズスクイブ社：講演料

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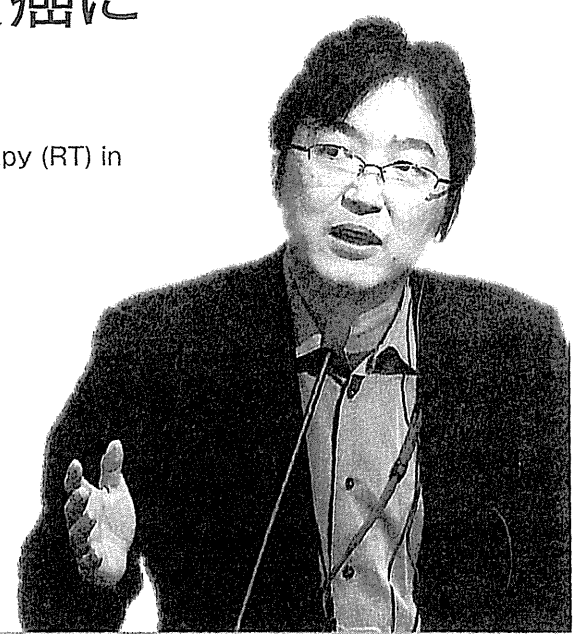
Plenary Session ―― 6

局所進行頭頸部扁平上皮癌に対する国内第Ⅱ相試験

Phase Ⅱ study of Cetuximab with Concomitant boost Therapy (RT) in Japanese Patients with LA-SCCHN.



国立がん研究センター東病院臨床開発センター粒子線医学開発部分野医員
全田 貞幹

Summary

頭頸部癌は全悪性腫瘍の5.2%を占め増加が予想される癌であり，そのほとんどが局所進行頭頸部扁平上皮癌（LA-SCCHN）である。LA-SCCHNに対する放射線療法にセツキシマブを併用することは，海外第Ⅲ相試験（Bonner試験）で放射線療法単独よりも優越していることが示されている。わが国でも日本人に対しての安全性・有効性を確認するための国内第Ⅱ相試験（EMR62241-053）を2009年3月から2010年1月に実施した。

試験概要

基本的にBonner試験とほぼ同じであり，LA-SCCHNの中・下咽頭癌，喉頭癌のStageⅢ/Ⅳの患者を対象としている。セツキシマブを1週目に400mg/m^{2}を投与し，その後，週に1回250mg/m^{2}を維持投与した。放射線療法は1週遅れてスタートし，定型照射法によるconcomitant boostのみで，72Gy/42fractionsの照射を行った（図）。

主要評価項目は，Bonner試験が出ているが治療コンプライアンスとして70%以上のrelative dose intensity（RDI）と放射線療法の完遂率をみた。副次評価項目は奏効率で放射線治療終了後8～12週の間にCTとMRIを撮影し，Response Evaluation Criteria in Solid Tumors（RECIST）評価を行った。また安全性に関しては，Common Terminology Criteria for Adverse Events（CTCAE）Ver.3.0によって評価した。

結 果

登録した27名のうち22名の患者が解析対象となり，うち21名が男性であった（表）。年齢中央値は海外に比べて年齢層が高い67歳である。原発部位は中咽頭の割合が海外よりやや少ないがHPV陽性・陰性にかかわらず喫煙者が多いという結果になった。セツキシマブの投与状況については，RDIが90%を超えたものがほとんどで，少しスキップしたものも80%以上をキープしており，ほぼ

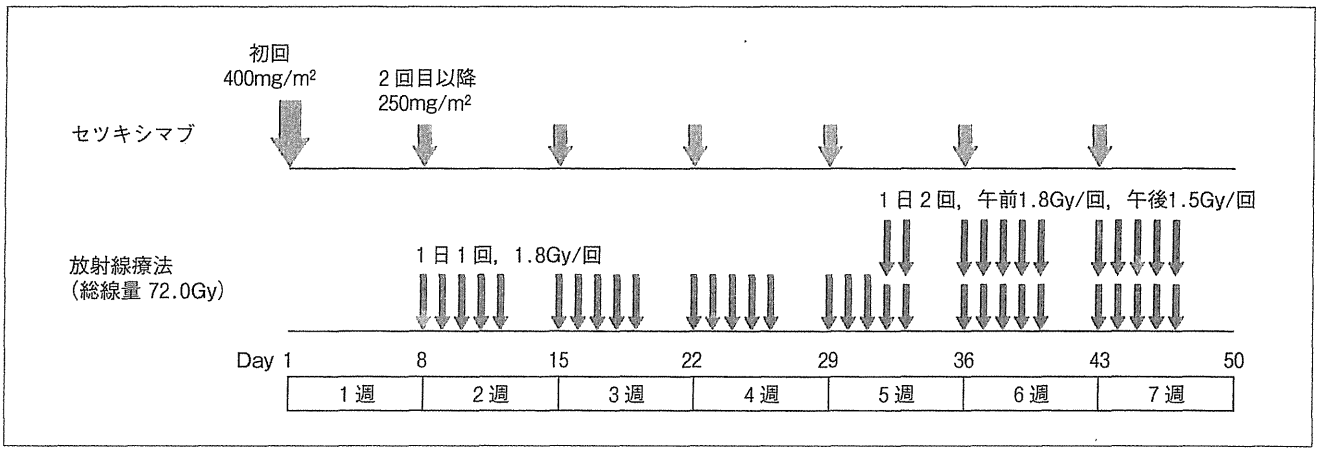


図 投与および照射スケジュール

（アービタックス®注射液100mg 適応追加，2012年12月）

表 患者背景

		全症例（ITT）（22例）
性別	男性	21（95.5%）
	女性	1（4.5%）
年齢（歳）	中央値（範囲）	67（53～81）
年齢区分	65歳未満	7（31.8%）
	65歳以上	15（68.2%）
KPS	90	8（36.4%）
	100	14（63.6%）
原発部位	中咽頭	6（27.3%）
	下咽頭	8（36.4%）
	喉頭	8（36.4%）

KPS：Karnofsy Performance Status

（アービタックス®注射液100mg 適応追加，2012年12月）

100%設定した基準を満たしていた。放射線療法については，毒性により長期の延期を要した患者はおらず，全例が72Gyを完遂した。

副次評価項目（放射線療法終了後8週目）の奏効率は81.8%であった。Bonner試験での放射線療法とセツキシマブの併用群の奏効率が73.5%であったことから，少なくとも日本のデータが劣っているわけではないことがわかる。

安全性についてはセツキシマブの特徴的な有害事象であるざ瘡様皮疹もしくは皮膚炎を呈したうち，3例に重篤な症状が出たが，治療の遅延に影響するほどではなかった。また，1例だけであったがinfusion related reactionがあり，おそらく国内では耳鼻咽喉科の先生が主に使用することを考えると，こういったinfusion reactionへの対応についても発信していく必要があると思われる。

ま と め

今回行った国内第II相試験は，22名のLA-SCCHNにおいて，放射線療法＋セツキシマブ併用療法のコンプライアンスは100%で，抗腫瘍効果の奏効率が80%を超えていた。副作用についても，日本人において特別な反応が起こるわけではないことがわかったため，今後は日本からも海外に情報を発信していくことが期待される。

質疑応答

Q1 Infusion reactionへの対応を教えてください。

Infusion reactionがみられたら，まずセツキシマブ投与を止めることが重要です。点滴をする際に必ずしも医師がいるとは限らないことを考えると，infusion reactionが起こる可能性があることを看護師にも情報共有し，注意喚起をすることが大切だと思います。

また，セツキシマブ投与を止めた後に使用する薬剤の指示などのマニュアルの作成をしておく，ステロイドを含んだ薬剤のセットを治療前に準備しておくなど，すぐに対応できるよう病院全体で共有するとよいと思います。

Q2 わが国でconcomitant boost法を用いた試験は唯一だと思うのですが，従来の通常分割に対して，局所制御の上乗せがあるのでしょうか。また，今回は強度変調放射線治療（IMRT）の装置ではなくて，従来の装置を使用されたのですか。

1日2回照射をすることの煩雑さなど種々の要素を考えると，IMRTで70Gy/33fractionsや70Gy/35fractionsの照射とさほどの差は出ない印象があります。実臨床ですべてconcomitant boost法で実施しないといけないとは思いません。Bonner試験に沿って行ったため1日2回照射を選んだのですが，装置は日本の水準を鑑みてIMRTではなく通常の3DRTで実施しました。

Q3 今回の試験はconcomitant boost法を用いて行われましたが，いま通常分割法が見直されていると個人的に思っています。今後，日本での照射法についてアドバイスをいただけますでしょうか（Ang先生に対して）。

Concomitant boost法はIMRTが普及する前に行われていた方法で，IMRTの普及とともに治療の迅速化と多分割のコンセプトを統合できるようになったため，現在はIMRT 70Gy/35fractions（7週間）を用いています。したがって，緻密なdose paintingによって正常組織への線量を低減できる照射を行うことで将来的にはIMRT 70Gy/30fractions（6週間）で完遂できるようになると思います（by Ang先生）。

JOHNS
特集●下咽頭癌はここまで治る●

QOL向上を目指して

放射線治療による有害事象軽減のための支持療法

全田貞幹*
Sadamoto ZENDA

● Key Words ●放射線治療，有害事象，粘膜炎，皮膚炎，支持療法●

はじめに

近年，進行下咽頭癌に対して喉頭温存を目的に化学放射線療法を選択する機会が多くなってきた。わが国における化学放射線療法ではその照射線量および抗癌薬の投与量は海外のそれに低く設定されている。一方毒性の頻度は同等もしくはそれ以上とされ，学会等では皮膚炎，口内炎・粘膜炎の出現による治療の休止や中止も多く報告されている。その原因として，人種差など患者側の問題を指摘する意見もあるが医療者側の問題として疼痛や皮膚炎などの対策を医師や看護師個人の判断に任せ，体系的な管理がうまくできていないことも考慮すべきである。

放射線治療は治療期間と抗腫瘍効果の関係[1]が指摘されており，安易に治療を休止することは治療成績の低下につながるためできるだけ避けなければならない。本稿では，各毒性に対して体系的な対策を講じることで予定通り治療を完遂することを目指すいくつかの支持療法について示し，その具体例について解説する。

Ⅰ．放射線治療中に起こる有害事象とその対策

有害事象の対策は大きく予防と対症に分けられ，それぞれの副作用についていずれかの方法をとるべきである。

1．口内炎・粘膜炎（図1）

口内炎・粘膜炎は下咽頭癌の放射線治療においては必発の副作用であるため，しっかりとした対策を立てればこれによる治療休止を最小限に抑えることができる。口内炎・粘膜炎の予防策については薬剤を用いた試験が検証されてきたが，予防することで治療効果に影響のある薬剤もあったため，現状臨床の現場では対症療法に専念することが勧められる。

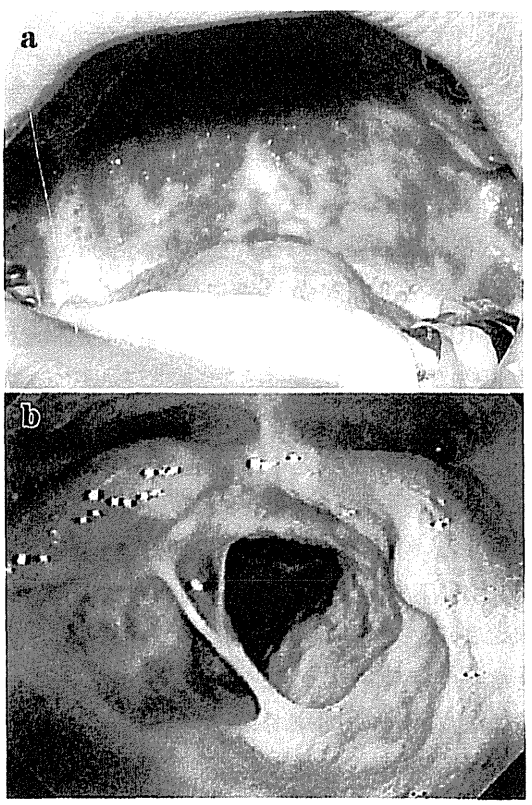


図1　口内炎（a）・粘膜炎（b）

本邦において他施設共同研究として疼痛管理に関する試験[2]が行われ，その結果が公表されている。その方法は“opioid based pain control program”（図2）と呼称され，確実な栄養・薬剤投与経路として胃瘻を造設し疼痛はモルヒネを主軸

* 国立がん研究センター東病院粒子線医学開発分野
〔〒277-8577 千葉県柏市柏の葉6-5-1〕

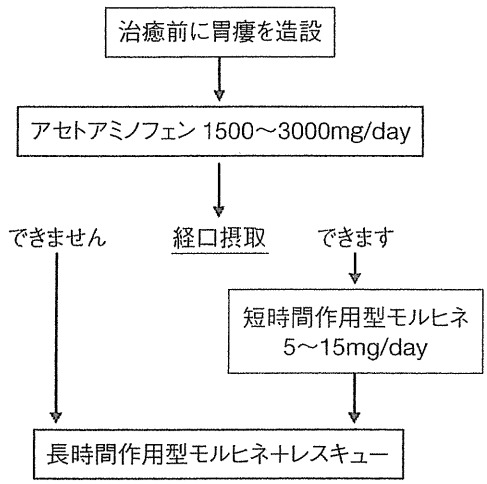


図 2　Opioid based pain control program

に管理していくというものであったが，この試験では放射線治療を予定外に中止した患者はわずか1例（0.9%）で休止率も12.7%（1週間以上の休止は0例）と治療完遂という点において優れた成績を報告している。

付随的なデータとして，化学放射線療法中にモルヒネが必要になる患者は約8割であり，使用するモルヒネの使用量の中央値は35 mg程度であった。NSAIDsはCDDPとの腎毒性で相乗効果が疑われるため，NSAIDsではなくモルヒネを使用するという点は理にかなっていると言える。

また，胃瘻に関するトラブルは治療中で4%程度と非常に低く，一方患者教育により退院して患者管理が可能になる割合は90%と非常に高かった。胃瘻についてはこの試験では治療前に造設している。海外では治療中に造設する施設もあり，各施設の事情にあったセッティングが必要と考える。

2．皮膚炎（図3）

皮膚炎も放射線治療を行っている患者には必発の副作用である。それ自体命に別状はないものの，管理をずさんにすると感染の引き金になったり，照射野に痕が残ってしまったりと患者のQOLに影響を及ぼす可能性が高いためしっかり対応する必要がある。皮膚炎の予防は現時点で有効なものはなく，対症療法に専念すべきである。

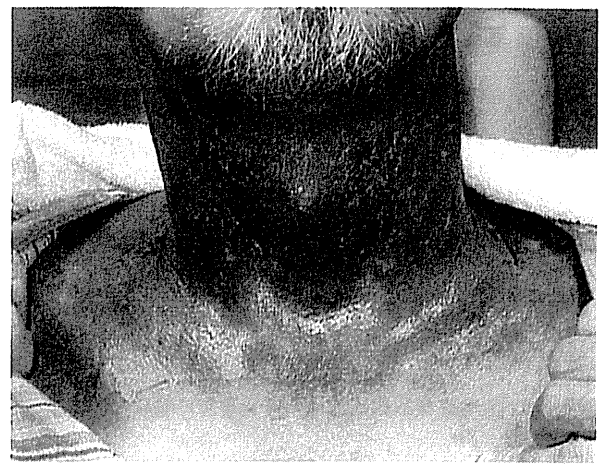


図 3　皮膚炎（グレード2）

皮膚炎管理の要則は，

1）照射野内の皮膚に対する刺激を避ける

2）清潔にする

3）保湿する

の3つである。

1）照射野内の皮膚に対する刺激を避ける

実臨床において皮膚炎予防を企図して照射早期から照射内に薬剤等を塗布することがあるが，その場合は物理的刺激による皮膚炎の増悪の可能性があることも念頭に置くべきである。

予防的な処置が皮膚炎軽減に寄与するというエビデンスはなく，また逆効果であると報告しているものもないため，予防的処置の有効性は学術的にはいまだ不明である。

2）清潔にする

皮膚炎の症状がだんだん強くなると患者やその家族はその部位にできるだけ触れないようにする傾向があり，その結果，照射野がやや不潔になってしまうことがある。Crustやガーゼの糸等を照射野に残しておくと感染の契機や創傷治癒遅延の原因となるため，洗浄した方がよい。

ヨードや過酸化水素水などで消毒すると組織が挫滅し，逆に創傷治癒が遅延するため消毒はしてはいけない。

3）保湿する

従来傷は乾燥させて治すとされてきたが，近年その発想は逆転し治癒した傷が乾燥することがわかってきた。湿性落屑は創傷治癒のために必要なサイトカインであり，これを拭き取って乾燥状態

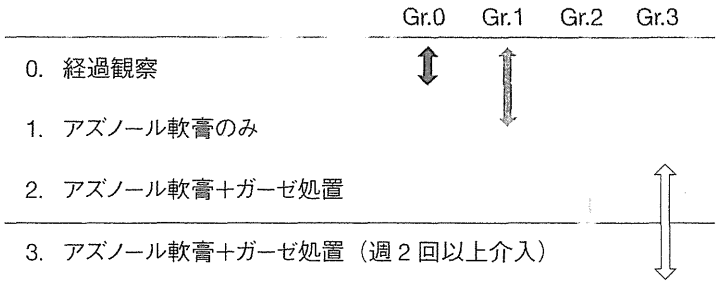


図 4　Dermatitis Control Program（DeCoP）

にすることは創傷治癒を遅延させる行為である。

傷を乾燥させるという方法は看護領域，一部の医師間でもまだ根強く残っているため，医師-看護師とよく連携し意思統一することが肝要である。

全田らは，上記の3つをプログラムに組み込んだ皮膚炎管理プログラム（Dermatitis Control Program：DeCoP）を開発し，前向きコホート試験[3]を行った（図4）。

根治的（化学）放射線治療を受けた113例の患者を対象にDeCoPで皮膚炎処置を行った結果，皮膚炎Gr.3の発現はわずかに9.7%と少なく，治療開始から2週間後には半数以上の患者に皮膚炎の回復が確認されたと報告している

ステロイド軟膏の使用については賛否両論ある[4,5]ところだが，ステロイドの有用性を示した臨床試験はなく，積極的な使用を勧める根拠は乏しい。しかしながらステロイドが無効であることを示したものもなく，長く慣例的に行われていることを考慮すると現時点では各施設の裁量に任せられるところである。

3．味覚障害

味覚障害については，栄養学や亜鉛の補正などさまざまな試みがなされているが，いずれも規模が小さく，決め手となるような研究はまだ成就していない。今後の取り組むべき課題と言える。

4．口内乾燥（唾液腺障害）

頭頸部の放射線治療を行った場合，口内乾燥は従来避けられない副作用であったが，近年薬剤や照射技術開発によるアプローチなど成果が出ているものもある。

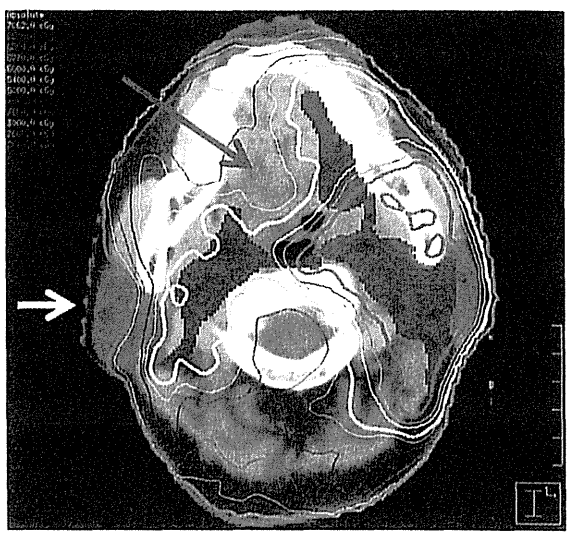


図 5　IMRTによる重要臓器の遮蔽
IMRTを用いた右唾液腺の遮蔽。
赤矢印：口腔内の線量を低減している
白矢印：右唾液腺を遮蔽している

1）内服薬（ピロカルピン塩酸塩）

ピロカルピン（商品名：サラジェン）は元々シェーグレン症候群による口腔乾燥に用いられていた薬剤であるが，これを放射線治療による口内乾燥に応用し奏効している症例もある。

副作用として多汗，鼻炎，下痢，頻尿，頭痛，ほてり，嘔気，悪寒などがあり，投与の継続に関しては，奏効しているかどうかに加え上記の副作用の強さによっても判断が必要である。

2）IMRT（強度変調放射線治療）

海外では既にこの手法がスタンダードであるが，日本では頭頸部領域でまだ1〜2割程度しか普及していない。

IMRTはその高度な照射技術で唾液腺自体を遮蔽することが可能[6]であり，最も効果的な口腔乾燥予防の手段である（**図5**）。

さいごに

強力な治療を行えば強い副作用が出ることはいわば当然のことであり，強力な治療と副作用対策はセットで考えなければ成立しない。逆に副作用を気にして本治療の強度を下げてしまうことは生存率の低下につながり，最終的には患者の不利益になりうる。新規の治療が開発されればそれに伴って対応する副作用処置を考えてしかるべきであり，そのようなバランス感覚も術者に求められるところである。

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Depressive symptoms after treatment in hepatocellular carcinoma survivors: prevalence, determinants, and impact on health-related quality of life

Naoko Mikoshiba[1]*, Mitsunori Miyashita[2], Tomoko Sakai[1], Ryosuke Tateishi[3] and Kazuhiko Koike[3]
[1]*Department of Adult Nursing/Palliative Care Nursing, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
[2]*Department of Palliative Nursing, Health Sciences, Graduate School of Medicine, Tohoku University, Sendai, Japan*
[3]*Department of Gastroenterology, The University of Tokyo, Tokyo, Japan*

**Correspondence to: Department of Adult Nursing/ Palliative Care Nursing, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. E-mail: naokom-tky@umin.ac.jp*

Abstract

***Objective*: The purposes of this study were to investigate the prevalence and determinants of depressive symptoms among hepatocellular carcinoma (HCC) survivors and to evaluate the impact of depressive symptoms on health-related quality of life (HRQOL).**

***Methods*: A cross-sectional study was conducted on 128 consecutive patients attending an outpatient clinic in Japan 1 year or more after curative treatment. To assess depressive symptoms and HRQOL, the participants were asked to complete the Center for Epidemiologic Studies Depressive Symptoms Scale, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and EORTC QLQ-HCC18, respectively. Multiple logistic regression models were used to identify factors associated with depressive symptoms. EORTC QLQ-C30 and EORTC QLQ-HCC18 scores were compared between participants with and without depressive symptoms.**

***Results*: The prevalence of depressive symptoms among the HCC survivors was 28.3%. The multiple logistic regression analysis revealed that the determinants of depressive symptoms included poor Karnofsky performance status (odds ratio [OR] = 4.59, 95% CI = 1.03–20.55, $p = 0.04$), poor liver function (OR = 3.22, 95% CI = 1.11–10.0, $p = 0.03$), living alone (OR = 6.87, 95% CI = 2.53–18.63, $p = 0.0002$), and unemployment (OR = 5.18, 95% CI = 1.73–15.54, $p = 0.003$). Survivors with depressive symptoms had poorer HRQOL in almost all domains compared with survivors with no depressive symptoms.**

***Conclusions*: This study suggests that after treatment, many HCC survivors experience depressive symptoms that are strongly associated with poorer HRQOL.**

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Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide [1]. It is the sixth most common malignancy in the world, with more than half a million new cases annually [1]. The HCC 5-year survival rate after liver resection or liver transplantation has reached over 50% because of improvements in diagnosis and treatment, and the number of HCC survivors has increased [2]. The HCC recurrence rate is very high because of chronic hepatitis, which is the predominant risk factor for HCC in China, Western countries, and Japan [2,3]. Therefore, it is becoming increasingly important to preserve health-related quality of life (HRQOL) of HCC patients during their prolonged life span.

It is known that many cancer survivors experience a number of symptoms and posttreatment effects, including depressive symptoms [4]. Although depressive symptom is a symptom that occurs during the course of cancer, it persists for years after the completion of treatment, and it is one of the most frequent symptoms experienced by cancer survivors [4,5]. It has been suggested that depressive symptoms strongly affect HRQOL [4,6] and can lead to a shorter survival of cancer patients [7,8]. Fortunately, depressive symptoms are treatable. Numerous randomized controlled trials show that psychological distress, including depressive symptoms, can be alleviated by pharmacologic and nonpharmacologic interventions [9]. Therefore, it is particularly important, for cancer survivors, to implement routine depressive symptoms screening and provide appropriate care and treatment.

Although research interest in depressive symptoms among cancer survivors has increased in recent decades, there have been no studies investigating depressive symptoms among HCC survivors. Therefore, little is known about the prevalence and causes of depressive symptoms among HCC survivors, or the characteristics of those most at risk of developing depressive symptoms. This situation makes it difficult to manage the problem. Thus, the aims of this study were to estimate the prevalence of depressive symptoms in HCC survivors more than 1-year posttreatment, to identify factors associated

with depressive symptoms, and to evaluate the impact of depressive symptoms on HRQOL.

Materials and methods

Data collection

We conducted a cross-sectional study of HCC survivors 1 year or more after HCC treatment (curative treatment). The HCC survivors were selected from patients who consecutively attended the Gastroenterology Outpatient Clinic of The University of Tokyo Hospital (a tertiary care teaching hospital). Patients went to see a doctor every 3 months to check for the recurrence of HCC. Patient medical records were reviewed prior to selecting potentially eligible patients. The eligibility criteria were as follows: (1) diagnosed with HCC more than 1 year prior to data collection and had curative treatment at The University of Tokyo Hospital; (2) able to communicate in Japanese; (3) able to participate in the study, as judged by an attending doctor; and (4) 20 years of age or older. Patients with evidence of metastatic or recurrent cancer, those with a history of other types of cancer, and those who were receiving cancer treatment were excluded from the study.

Data were collected after the patients' medical appointments from August 2008 to August 2009 by one of the investigators. Patients self-administered the questionnaires. Medical data were collected by reviewing the patients' medical care records. The investigator checked for absent responses after receiving the questionnaire and when possible, asked the patients to respond to missing items. The ethics committee of The University of Tokyo approved this study, and all participants provided their written informed consent.

Measurement of depressive symptoms

Depressive symptoms were measured using the Japanese version of the Center for Epidemiologic Studies Depressive Symptoms Scale (CES-D) [10]. The CES-D is a 20-item self-report questionnaire designed for the screening of depressive symptoms. Scores for each item are summed to give a range of total scores from 0 to 60. A higher score indicates a greater tendency toward depressive symptoms. A score of 16 points or higher suggests the presence of clinical depressive symptoms [10]. The reliability and validity of the Japanese version of the CES-D have been confirmed [10]. In the Japanese version, the cutoff value of 16 was also optimal, assessed by comparing the proportion of patients with CES-D score of 16 points or higher in a normal control group with that in a group of patients with mood disorders [10].

Measurement of health-related quality of life

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) is a questionnaire for assessing HRQOL of cancer patients. The self-administered questionnaire includes a total of 30 items and includes six functioning scales: physical (five items), emotional (four items), role (two items), cognitive (two items), and social functioning (two items), as well as global health status (two items). The questionnaire also includes three symptom scales: vomiting (two items), fatigue (three items), and pain (two items). Six single items assess dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The global health status items are rated from 1 (very poor) to 7 (excellent), and the remaining items are rated 1 (not at all) to 4 (very much). All item response scores were converted into 0–100 scores according to the EORTC scoring guidelines. Higher scores mean a better function or a worse symptom. The reliability and validity of the Japanese version of the EORTC QLQ-C30 have been confirmed [11].

The EORTC QLQ-HCC18 is an HCC-specific supplemental module developed to augment QLQ-C30 and to enhance the sensitivity and specificity of HCC-related QOL issues [12,13]. The self-administered questionnaire includes a total of 18 items and includes six multi-item scales: fatigue (three items), body image (two items), jaundice (two items), nutrition (five items), pain (two items), and fever (two items). Two single items assess sexual life and abdominal swelling. The items are rated 1 (not at all) to 4 (very much). The scales and items are linearly transformed to a 0–100 score, where 100 represents the worst status. The reliability and validity of the Japanese version of the EORTC QLQ-HCC18 have been confirmed [14].

Sociodemographic characteristics

The following sociodemographic information was collected from the self-administered questionnaire: gender, age, employment status, educational level, and cohabitation status.

Clinical characteristics

The following clinical information was collected from the patients' medical records: Karnofsky performance status (KPS), etiology of liver disease, comorbidity other than chronic liver disease, liver function (Child–Pugh grade), history of HCC recurrence after initial treatment, and time since treatment. Higher scores in KPS signify better performance status. We placed cutoff value at 80 points, where patients begin to feel difficulties in normal activity or work. Liver function becomes worse in alphabetical order of Child–Pugh grades A, B, and C.

Statistical analysis

Descriptive statistics are used to present the prevalence of depressive symptoms and the characteristics of the participants. The prevalence of depressive symptoms was

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determined by calculating the proportion of patients exhibiting a score of 16 points or higher on the CES-D.

We used *t*-tests to compare the EORTC QLQ-C30 and EORTC QLQ-HCC18 domain scores between the HCC survivors with depressive symptoms and those with no depressive symptoms. The clinical relevance of the difference in the mean scores of HRQOL scales between groups was further measured by calculating the effect size using Cohen's *d* coefficient. As recommended [15], we considered *d* values less than 0.2, anything above 0.2 but less than 0.5, and anything at or above 0.5 as indicating small, moderate, and large effect sizes, respectively. Chi-squared tests, Fisher's exact tests, and *t*-tests were used to compare CES-D scores among sociodemographic and clinical variables, as appropriate. To identify the sociodemographic and clinical variables that were independently associated with depressive symptoms, multivariate logistic regression models were used. Variables with a p value of 0.2 or less were included in a backward variable selection. Odds ratios and 95% CIs were calculated for each variable in the final model. In all statistical tests, $p < 0.05$ (two-sided) was regarded as statistically significant. Statistical analyses were performed using SAS release 9.2 (SAS institute Inc., Cary NC, USA).

Results

Among 128 eligible patients, one refused to participate (because of a lack of time). Thus, data from 127 patients were included in this study, a response rate of 99.2%. There were no missing data at the item or scale level.

Table 1. Sociodemographic and clinical characteristics of the study subjects

Variable	n (%)
Male gender	81 (63.7)
Age (years)[a]	69.0 ± 8.4
Employed full time or part-time	50 (39.4)
Education	
≤12 years	83 (65.3)
Living with family or other adults	85 (66.9)
Karnofsky performance status	
80–100	113 (88.9)
Etiology of liver disease	
Hepatitis C virus	75 (59.0)
Hepatitis B virus	43 (33.9)
Comorbidity other than chronic liver disease	
Yes	83 (65.4)
Child–Pugh grade	
A	96 (75.5)
History of HCC recurrence after initial treatment	
Yes	87 (68.5)
Time since treatment (months)[a]	24.7 ± 18.5

Values are expressed as numbers (%) unless otherwise specified.
HCC, hepatocellular carcinoma.
[a]Data are expressed as mean (standard deviation). Higher Karnofsky performance scores signify better performance status. Liver function becomes worse with increasing Child–Pugh grades A, B, and C.

Sociodemographic and clinical characteristics of the study subjects

Table 1 presents the sociodemographic and clinical characteristics of the study subjects. Most patients were men (63.7%), had good performance status (88.9%), and had good liver function (75.5%). The mean age of survivors was 69.0 years (standard deviation [SD] = 8.4), and the average time since treatment was 24.7 months (SD = 18.5).

Characteristics of hepatocellular carcinoma survivors by depressive symptoms group

Using the dichotomous cutoff (CES-D score ≥ 16), 36 (28.3%) survivors were classified as having depressive symptoms. The average CES-D score was 21.9 (SD = 7.3, median = 20) and 8.5 (SD = 4.1, median = 9) for survivors with and without depressive symptoms, respectively. Table 2 presents the distribution of HCC survivors by depressive symptoms group. The mean age of survivors in the depressive symptoms group was 71.1 years (SD = 7.6). The mean age of survivors in the no-depressive symptoms group was 68.2 years (SD = 8.6).

There were significant differences in KPS scores, Child–Pugh grades, cohabitation, and employment between the two depressive symptoms groups. There were no differences between the depressive symptoms groups in terms of gender, age, etiology of liver disease, education, history of HCC recurrence after initial treatment, and time since treatment.

Multivariate logistic regression models of depressive symptoms

By using multivariate logistic regression procedures, four significant determinants of depressive symptoms were identified (Table 3). Having KPS scores less than 80, having Child–Pugh grade B or C, living alone, and being unemployed were associated with an increased likelihood of depressive symptoms. Multivariate logistic regression analysis with adjustment for age [16–19], KPS [16,20,21], and time since treatment [22,23], which are considered to be important factors related to depressive symptoms, yielded same results.

Depressive symptoms and health-related quality of life

The EORTC QLQ-C30 and EORTC QLQ-HCC18 scores by depressive symptoms groups are presented in Table 4. The HRQOL scores were significantly lower among HCC survivors with depressive symptoms than among survivors with no depressive symptoms in almost all domains, and the effect size was medium or large in all domains except for sexual interest. In addition to univariate analysis, we conducted a multivariate regression analysis with adjustment for age [24–26], gender [27], KPS [28], Child–Pugh grade [27,29,30], and history of

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Table 2. Characteristics of hepatocellular carcinoma survivors by depressive symptoms group

Variables	CES-D score: Depressive symptoms ($n=36$)	CES-D score: No depressive symptoms ($n=91$)	p-value
Gender			0.05
Male	18 (50.0)	63 (69.2)	
Female	18 (50.0)	28 (30.8)	
Age (years)[a]	71.1 ± 7.6	68.2 ± 8.6	0.08
Employment status			0.001
Employed	6 (16.7)	44 (48.3)	
Unemployed	30 (83.3)	47 (51.7)	
Education			0.11
≤12 years	13 (36.1)	70 (76.9)	
>12 years	23 (63.9)	21 (23.1)	
Cohabitation status			<0.0001
Living with family or other adults	15 (41.6)	70 (76.9)	
Living alone	21 (58.4)	21 (23.1)	
Karnofsky performance status			<0.0001
80–100	26 (72.2)	87 (95.6)	
Less than 80	10 (27.8)	4 (4.4)	
Etiology of liver disease			
Hepatitis C virus			0.27
Yes	24 (66.7)	51 (56.0)	
No	12 (33.3)	40 (44.0)	
Hepatitis B virus			0.93
Yes	12 (33.3)	31 (34.1)	
No	24 (66.7)	60 (65.9)	
Comorbidity other than chronic liver disease			0.31
Yes	26 (72.2)	57 (62.6)	
No	10 (27.8)	34 (37.4)	
Child–Pugh grade			<0.0001
A	20 (55.6)	76 (83.5)	
B/C	16 (44.4)	15 (16.5)	
History of HCC recurrence after initial treatment			0.78
Yes	24 (66.7)	63 (69.2)	
No	12 (33.3)	28 (30.8)	
Time since treatment, months[a]	27.3 ± 18.7	27.6 ± 18.4	0.34

Values are expressed as numbers (%) unless otherwise specified. Higher Karnofsky performance scores signify better performance status. Liver function becomes worse with increasing Child–Pugh grades A, B, and C. CES-D, Center for Epidemiologic Studies Depressive symptoms Scale; HCC, hepatocellular carcinoma.
[a]Data are expressed as mean (standard deviation).

Table 3. Multivariate logistic regression model for depressive symptoms in hepatocellular carcinoma survivors

Variable	Adjusted OR	95% CI	p-value
KPS			
Less than 80	4.59	1.03–20.35	0.04
80–100 (ref)	1.00		
Child–Pugh grade			
B/C	3.22	1.11–10.0	0.03
A (ref)	1.00		
Cohabitation status			
Living alone	6.87	2.53–18.63	<0.001
Living with family or other adults (ref)	1.00		
Employment status			
Unemployed	5.18	1.73–15.54	0.003
Employed (ref)	1.00		

OR, odds ratio; KPS, Karnofsky performance status.

HCC recurrence after initial treatment [25,26,29], which are considered to be important factors related to HRQOL in HCC patients. As expected, depressive symptoms were independent factors related to almost all domains of HRQOL.

Discussion

To our knowledge, this is the first study that investigated the prevalence and determinants of depressive symptoms among the HCC survivors after their curative treatment. And this is the first study to investigate the impact of depressive symptoms on HRQOL precisely, using HCC-specific module. The prevalence of depressive symptoms among the HCC survivors was 28.3%. The multiple logistic regression

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Table 4. Comparison of EORTC QLQ-C30 and EORTC QLQ-HCC18 scores between HCC survivor depressive symptoms groups

	Depressive symptoms ($n=36$)	No depressive symptoms ($n=91$)	Effect size[a]	p-value
EORTC QLQ-C30[b]				
Global health status/QOL[c]	50.9 ± 18.9	73.8 ± 17.7	1.25[d]	<0.0001
Functional scales[c]				
Physical function	72.0 ± 19.8	89.6 ± 11.6	1.08[d]	<0.0001
Role function	69.4 ± 28.3	91.0 ± 15.8	0.94[d]	<0.0001
Emotional function	71.5 ± 20.4	89.6 ± 12.0	1.08[d]	<0.0001
Cognitive function	64.8 ± 26.6	80.7 ± 17.0	0.71[d]	0.0007
Social function	75.5 ± 25.6	91.4 ± 15.8	0.75[d]	0.0002
Symptom scales[e]				
Fatigue	44.7 ± 23.1	24.3 ± 18.5	0.97[d]	<0.0001
Pain	26.8 ± 13.8	6.4 ± 29.6	0.88[d]	0.0003
Nausea/vomiting	3.7 ± 6.4	1.5 ± 8.1	0.30[f]	0.14
Dyspnea	25.9 ± 25.3	12.8 ± 19.0	0.59[d]	0.007
Appetite	25.9 ± 31.9	8.8 ± 19.1	0.65[d]	0.004
Insomnia	35.2 ± 34.7	14.3 ± 20.6	0.73[d]	0.001
Constipation	22.2 ± 20.2	12.1 ± 29.8	0.39[f]	0.06
Diarrhea	13.9 ± 23.1	6.9 ± 31.9	0.25[f]	0.10
Financial difficulties	22.2 ± 31.9	10.9 ± 31.9	0.35[f]	0.05
EORTC QLQ-HCC18[b]				
Symptom scales[e]				
Fatigue	39.5 ± 24.6	20.0 ± 18.0	0.90[d]	<0.0001
Body image	42.1 ± 28.8	22.9 ± 19.9	0.77[d]	0.0006
Jaundice	21.2 ± 16.9	10.4 ± 13.9	0.69[d]	0.006
Nutrition	22.4 ± 18.5	9.7 ± 9.8	0.86[d]	0.0004
Pain	22.2 ± 16.4	10.4 ± 13.1	0.79[d]	0.0003
Fever	9.7 ± 14.6	2.6 ± 7.8	0.60[d]	0.007
Abdominal swelling	34.3 ± 31.4	12.4 ± 18.4	0.85[d]	0.0003
Sexual interest	11.4 ± 22.8	8.4 ± 22.3	0.13[g]	0.51

Data are expressed as mean ± standard deviation.
QOL, quality of life; EORTC, European Organization for Research and Treatment of Cancer.
[a]Cohen's *d*.
[b]Scale scores range from 0 to 100.
[c]Higher score indicates higher QOL.
[d]Large effect size.
[e]Higher score indicates lower QOL.
[f]Medium effect size.
[g]Small effect size.

analysis revealed that the determinants of depressive symptoms included poor KPS, poor liver function, living alone, and unemployment. Survivors with depressive symptoms had poorer HRQOL in almost all domains compared with survivors with no depressive symptoms.

The prevalence of depressive symptoms (28.3%) among the HCC survivors was slightly higher than that reported for other liver diseases, such as chronic liver disease (23.6%) [31] and hepatitis C (20.0–28.0%) [32,33]. The patients in this study continued to suffer from hepatitis or cirrhosis even after being treated for HCC. Furthermore, specific problems, such as the burden of other symptoms, the uncertainty of treatment outcomes, the fear of recurrence, and the probable change in socioeconomic status, may contribute to depressive symptoms in cancer survivors [34]. These factors may be responsible for the observation of a higher prevalence of depressive symptoms in HCC survivors compared with that observed in chronic liver disease or hepatitis C patients.

The prevalence of depressive symptoms among the HCC survivors was higher than that reported among survivors of prostate cancer (17.0%) [35] or breast cancer (23.0%) [36] but lower than that reported among survivors of colorectal cancer (36.7%) [6]. Colorectal cancer survivors may have associated changes in bowel habit, and sexual or micturition problems after surgery, leading to a higher prevalence of depressive symptoms among them. Colorectal cancer patients undergo postoperative adjuvant therapy such as chemotherapy or radiotherapy. Although postoperative loss of function and the symptoms caused by adjuvant therapy are thought to contribute to depressive symptoms in other cancer survivors, HCC patients rarely undergo adjuvant therapy, and no functions are lost through treatment. Nevertheless, the fact that the prevalence of depressive symptoms among HCC survivors is similar to or higher than that among other cancer survivors indicates the need to take precautions against depressive symptoms in HCC patients.

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To increase our knowledge of the factors associated with depressive symptoms among HCC survivors, we compared the depressive symptoms groups with a variety of sociodemographic and clinical variables. Our results indicate that sociodemographic and psychosocial variables such as living alone and being unemployed, in addition to physical variables such as poor KPS and decreased liver function, were associated with depressive symptoms. Previous studies with survivors of other cancers have identified physical [19,37], sociodemographic [17,38], and psychosocial variables [20,39–42] and modifiable health behaviors [43] to be important factors associated with depressive symptoms. We found these to be true for the survivors of HCC in our study and found that poor liver function was an HCC survivor-specific factor associated with depressive symptoms. HCC survivors continue to suffer from hepatitis or cirrhosis after curative treatment for HCC. With the progression of liver cirrhosis, they suffer from ascites, hepatic encephalopathy, and various physical symptoms, which may contribute to a higher psychological distress than other cancers. Healthcare professionals need to keep a close eye on the decrease of liver function after curative treatment.

Previous studies regarding the survivors of various types of cancer have indicated that depressive symptoms are associated to HRQOL [4]. In our study, we showed that depressive symptoms are strongly related to almost all domains of EORTC QLQ-C30 and HCC-specific module, EORTC QLQ-HCC18. The effect size was medium or large in all domains except for sexual interest, suggesting a big difference between individuals with depressive symptoms and those without. Thus, continuous screening for depressive symptoms of HCC survivors is warranted because it is a symptom that healthcare professionals tend to underestimate [44].

Our study was subject to some limitations. First, it was of cross-sectional design; therefore, no causal relations among the variables and depressive symptoms could be established. The study was conducted on a small number of HCC survivors at one hospital, and therefore, the findings may not be generalized to other populations. Second, we did not perform standardized psychiatric interviews; however, the CES-D has been shown to be a reliable and valid screening instrument for depressive symptoms. Third, we could not include age-matched and gender-matched noncancer control. This would be the subject for our further research. Fourth, we could not include variables such as mental disorder prior to cancer and health behavior. Future research should evaluate additional variables related to depressive symptoms following HCC treatment and their impact on HRQOL. Fifth, depressive symptoms and HRQOL based on the type of treatments received could not be explored in this study, as patients had varying treatment durations, types of treatment, and times between treatments.

Despite these limitations, this study contributes to highlight a potential target group for the intervention to prevent and treat depressive symptoms in HCC survivors.

Conclusion

This study found that many HCC survivors experienced depressive symptoms after their curative treatment. Depressive symptoms were influenced by sociodemographic and clinical factors and had a negative impact on HRQOL, with poorer scores in almost all domains among patients with depressive symptoms. Healthcare professionals should pay more attention to the possibility of depressive symptoms among HCC survivors with poor KPS, poor liver function, who live alone, and/or are unemployed. Interventions for depressive symptoms among patients with cancer have been shown to be effective; therefore, we believe that implementing a program geared toward HCC patients and survivors would be beneficial. Because multiple physical and social factors were associated with depressive symptoms among the HCC survivors, it is important to provide comprehensive interdisciplinary interventions in addition to normal treatment for depressive symptoms. Future research should evaluate additional variables related to depressive symptoms following HCC treatment and their impact on HRQOL over time.

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Conflict of interest

The authors of this study did not receive any financial support for this study and declare no conflict of interest.

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