常のCPU計算に比べて10倍以上の高速化を達成できた。

D. 考察

線量計算法の実臨床応用に当たり、患者条件により、エネルギーや拡大ブラッグピーク幅、ボーラス形状、患者コリメータ形状など照射条件は大きく異なることから、ファントムを用いた線量検証が必要と考える。

また、一般に、モンテカルロ法は計算時間がかかり過ぎるために、臨床利用が厳しいとされてきた。しかしながら、今回、我々は、計算速度について、従来の計算時間とほとんど大差ないレベルまで到達することに成功できた。それゆえ、今回の成果により、臨床利用時に計算時間が問題となることはなくなったと考える。そして、今回開発されたSMC法を、臨床解析やモニタユニット計算など如何に活用して行くかが、今後の課題となる。

E. 結論

ワブラー照射法に対するSMC法を開発し、治療計画装置に実装した。また、GPGPUによるSMC法の高速化を図り、SMC法の臨床利用に目処が付いた。

F. 研究発表

1. 論文発表

該当無し

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G. 知的財産権の出願・登録状況
(予定を含む)

1. 特許取得
特願2014-116974

2. 実用新案登録
なし

3. その他
なし

厚生労働科学研究委託費（革新的がん医療実用化研究事業）
委託業務成果報告（総括・業務項目）

更なる低侵襲化を目指した強度変調陽子線照射システムの技術開発
陽子線治療計画装置の開発及び医学物理的研究開発検討

担当責任者　堀田　健二
国立がん研究センター東病院　粒子線医学開発分野　医学物理士

研究要旨
陽子線治療の長所を最大限活用できる治療計画装置開発のため、処方線量設定機能とROI入力機能の追加開発を行った。追加した機能が問題なく動作することを確認したが、処方線量設定には5%程度の誤差が残った。今後の課題として線量計算精度の向上を図り、精度検証を実施する予定である

A．研究目的
陽子線治療の長所を最大限活用するための治療計画装置を開発する。高精度かつ高速な線量計算アルゴリズムにより、治療計画と治療結果との正確な対応付けを可能にする。また、適当なビーム配置を設計するための諸機能を搭載することで、限られた治療準備期間での最適な治療計画立案を実現するため強度変調陽子線治療法での利用に先駆けて、拡大ビーム法での開発と精度検証を実施した。

B．研究方法
(1)処方線量設定機能の開発
陽子線治療ではアイソセンターへ治療線量を付与する処方を採用し、これに必要なモニタ値(MU: Monitor Unit)を実測に基づいて決定する方法が一般的である。このため処方のバリエーションが制限され、また人体を模した均質ファントム中でしか処方線量を管理できない。そこで実照射器のビーム出力と治療計画上の計算値を対応づけるテーブルを用意することで、治療計画装置上で処方線量を設定できる機能を開発した。過去の線量測定データを比較し、計算精度を検証した。
(2)ROI 入力機能の追加開発
治療計画は治療計画 CT 上に入力した ROI(Region of Interest)に対して最適化される。短時間で最適な治療計画を立案するために ROI 入力機能を追加した。例として、2 つ以上の ROI を合成する機能、治療寝台置換機能がある。追加機能の動作確認と、他の機能への干渉がないことを確認した。

C．研究結果
(1)処方線量設定機能の開発
現行法であるアイソセンターへの線量処方に関して、実測と計算との差を 40 症例で評価した結果、最大で 5%程度の誤差で一致した。また、計画装置上で絶対線量を計算できるようになったことで線量処方の自由度が向上し、アイソセンターへの線量処方、任意の点への線量処方、治療体積への線量処方を選択できるようになった。

(2)ROI 入力機能の追加開発

追加した機能の動作に問題はなく、他の機能への干渉がないことを確認できた。この機能により必要な ROI を簡便に入力できるようになった。

D. 考察

処方線量設定機能の計算精度について、照射野が小さい症例で実測との差異が見られたことから、照射野効果によるものと考えられる。今後 Clarkson 積分法の応用により線量計算精度の向上を図る。

E. 結論

処方線量設定機能と ROI 入力機能の追加開発を行った。追加した機能は他の機能への干渉もなく、問題なく動作することを確認した。処方線量設定機能については、実測との差異が見られたため、線量計算精度の向上を図る。また、体内不均一中での線量処方精度の評価を検討する。治療計画装置の機能向上の効果を拡大ビーム法で確認したのち、スキャニング法への展開を図る。

F. 研究発表

3. 論文発表

なし

4. 学会発表

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G. 知的財産権の出願・登録状況

4. 特許取得

なし

5. 実用新案登録

なし

6. その他

なし

厚生労働科学研究委託費（革新的がん医療実用化研究事業）
委託業務成果報告（業務項目）

更なる低侵襲化を目指した強度変調陽子線照射システムの技術開発
陽子線治療計画装置のコミッショニング

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研究要旨

陽子線治療計画装置のコミッショニングとして、開発された機能を確認し、線量検証を実施した。基本的機能の動作に大きな問題はなかったが、臨床利用時の利便性を考え、いくつかの機能の改善・追加を行った。線量検証では、単純な固体ファントムと２次元検出器を使い、測定を行った。その結果概ね問題はなかった。引き続き、様々な照射条件毎の線量検証を実施していく予定である。

A. 研究目的

現在開発中の陽子線治療計画装置を臨床利用するために、開発された機能を確認し、線量検証を実施する。臨床利用時における操作性を考慮し、さらに必要な機能改善を行い、その上、精度や許容範囲を評価することを目的とする。

B. 研究方法

ROI機能や表示機能、線量計算機能等の治療計画装置機能に対して、動作試験を実施した。基本的機能の確認に加え、想定される誤操作に対する抑止機能の確認を行った。

また、臨床利用時には、時間の限られた中、速やかに計画を立てなければならないので、効率的かつ直観的に操作できるようになっているかといった操作性も含めて確認を行った。

さらに、線量計算に関しては、2次元検出器を用いて線量検証を行った。

（倫理面への配慮）

本研究では技術機器開発を目的としているため臨床利用は実施しない。開発研究が進み動物および臨床利用に至った場合は、研究対象者に対してはヘルシンキ宣言に則し、臨床研究に関する倫理指針に沿い、人権擁護上の配慮、不利益・危険性の排除や説明と同意（インフォームド・コンセント）を徹底する。動物実験においては、動物愛護上の配慮を指針に基づき実施する。尚、画像データ等は個人情報保護法に基づいた国立がん研究センターの規定に則し、十分な管理体制を構築した上で取り扱う。

C. 研究結果

今期開発した治療計画装置に対して、動作検証を完了した。検証の結果、いくつかの機

能を改善・追加を行った。主なもの2点について、下記に述べる。

(1)ビームコピー機能の追加

治療期間中に腫瘍の変形や縮小が生じる場合がある。そのような症例に対しては、CTを再撮影し、引き続き同じ照射条件で治療を続けた場合、線量分布がどう変化するか評価する必要がある。その評価のために現在の照射条件を再撮影したCT画像に適用して、線量分布の再計算を行うためのビームコピー機能を追加した。

(2)照射線計算・表示機能改善

陽子線の照射方向の決定には、腫瘍の形やリスク臓器との位置関係を把握する必要がある。最適な照射角度を視覚でとらえられるように表示機能を改善した。

線量検証については、単純な形状の固体ファントムを用いた計画を立て、2次元検出器を用いて測定を行った。その結果、概ね問題はなかったが、さらなる精度向上のためには、治療計画装置に登録してある基準線量データを再評価する必要があった。

D. 考察

基本的機能、改善・追加された機能に大きな問題はなかった。線量検証を行うにあたっては、開発中の治療計画装置を、臨床利用中である当院の陽子線照射システム系に接続する必要があったため、接続試験や照射データ転送試験など、多くの試験段階を踏んで実行した。不具合はその都度修正し、治療システム全体の動作確認も行うことができた。

E. 結論

基本的機能、基準線量データに大きな問題はなかった。機能については、臨床利用時を想定しながら、今後も適宜改修が必要になると考える。また、線量検証については、実際は様々な照射条件により治療が実施されるので、様々な照射条件毎の線量検証は引き続き実施する必要があると考える。

F. 研究発表

5. 論文発表

なし

6. 学会発表

なし

G. 知的財産権の出願・登録状況

7. 特許取得

なし

8. 実用新案登録

なし

9. その他

なし

厚生労働科学研究委託費(革新的がん医療実用化研究事業)
委託業務成果報告(業務項目)

臨床的検討

研究開発分担者　林　隆一　国立がん研究センター東病院

研究要旨

本研究で開発を目指している治療技術の臨床応用で期待される効果は、IMRTでは治療可能でも陽子線治療では適応が難しい中下咽頭癌などを始めとする複雑な腫瘍形状を有する疾患への適応拡大である。陽子線治療による強度変調照射法が可能になればIMRTを凌駕する線量分布が実現でき、これらの問題への有効な解決方法となる。この実現に向けて、1)IMRTを含めた臨床的な問題点の明確化、2)スキャニング照射法の臨床的安全性・有効性検証、などに加えて、頭頚部外科の観点からの頭頸部癌の進展様式などの特性解析など段階を踏んで研究を進めていく。

林　隆一・国立がん研究センター東病院
頭頚部外科・科長　副院長

A. 研究目的

本研究では粒子線治療の中で化学療法併用効果が期待でき、局所進行癌への適応拡大が期待される陽子線治療を用いた強度変調陽子線治療法の実現に向けた以下の技術開発を行い、臨床応用への道筋をつけることを主目的とする。1)組織の不均質性に対応したモンテカルロ法を用いた治療計画の高精度化の開発、2)治療室内設置のコーンビームCT・in-room CT装置による腫瘍の位置・形状に応じた高速・高精度線量計算による治療計画と治療を実現するハードウェアおよびソフトウェアの包括的な治療技術開発。これらの技術開発に平行して、強度変調陽子線治療法の臨床的な有効性を明らかにするために、IMRTなどとの線量分布比較やその利点、欠点を明確にして、技術開発へフォードバックする。併せてスキャニング照射法の臨床試験実施のための準備を進める。

B. 研究方法

上記の研究開発に加えて画像誘導強度変調陽子線治療の臨床試験開始向けて、

その妥当性と臨床的な有効性を評価する臨床研究を今年中に立案・実施する。IMRTなどのX線による放射線治療の臨床的な問題点や改善点を明確化と陽子線治療の臨床データや線量分布の解析について頭頸部癌を対象に行い、スキャニング照射法ならびに画像誘導強度変調陽子線治療法の臨床的有効性の妥当性、適応疾患とそれに応じた治療デザインなどを検討する。加えて、切除例の解析結果を基礎に頭頸部癌の進展様式や病巣進展に基づいた問題点を明らかにして、強度変調放射線治療(IMRT)などのX線による放射線治療の臨床的な問題点や改善点を明確化する。

(倫理面への配慮)

本研究では技術機器開発を目的としているため臨床利用は実施しない。開発研究が進み動物および臨床利用に至った場合は、研究対象者に対してはヘルシンキ宣言に則し、臨床研究に関する倫理指針に沿い、人権擁護上の配慮、不利益・危険性の排除や説明と同意(インフォームド・コンセント)を徹底する。動物実験においては、動物愛護上の配慮を指針に基づき実施する。尚、画像データ等は個人情報保護法に基づいた国立がん研究センターの規定に則し、十分な管理体制を構築した上で取り扱う

C. 研究結果

今年度は以下の研究を実施して、一定の結果を得ている。1)頭頸部癌、特に頸部リンパ節転移を有する複雑形状に対する線量分布比較の基礎となるIMRTの線量分布を中心に、ターゲットへの線量とリスク臓器への線量低減のバランスについて、これまでの治療例を中心に解析を実施した。臨床成績、有害事象と線量分布との相関については、論文化をして現在投稿中である。2)強度変調陽子線治療実施の前段階となるスキャニング照射については、前立腺を対象に輪郭入力の最適化作業を行い、ターゲットへの線量を維持しつつリスク臓器の一つである直著線量の低減について検討した。その結果、現在のブロードビーム法に比較して、直腸線量、特に前壁の有意な線量低減が可能であることを確認した。その結果をもとに局所限局性前立腺癌に対するラインスキャニング照射法の安全性と有効性を検証する臨床試験のプロトコールを作成中で、来年度前半での実施を目指して準備を進めている。

D. 考察

スキャニング照射による線量分布のフレキシビリティー向上を確認し、その発展型である強度変調陽子線治療の有効性の臨床的な可能性が確認されつつある。まだ実施途中であるが、有効性とともに臨床的な限界なども明確にして、臨床での有効性検証のモデルを確立することを目指

す。

E. 結論

F. 健康危険情報
該当する事項はない。

G. 研究発表
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2. 学会発表
1) Hayashi R. Outcomes of cases with simultaneous resection of the thoracic esophageal cancer with other head and neck cancer resection followed by free flap reconstruction. IFHNOS. 2015

H. 知的財産権の出願・登録状況
該当する事項はない。

III. 学会等発表実績

1. 学会等における口頭・ポスター発表

発表した成果(発表題目、口頭・ポスター発表の別)	発表者氏名	発表した場所(学会等名)	発表した時期	国内・外の別
粒子線治療の特徴と今後の展望	秋元哲夫	日本臨床腫瘍学会	2014	国内
Hypofractionated image guided-IMRT for clinically localized prostate cancer.	Hashimoto Y, Akimoto T, Mitsuhashi N, et al	American Society for Radiation Oncology	2014	国外
Acute toxicities and DVH parameters for organ at risk in proton beam therapy for stage III non-small cell lung cancer.	Motegi A, Akimoto T, Niho S, et al	American Society for Radiation Oncology	2014	国外
生物学的アプローチと放射線治療の臨床 ー医学物理学的な進歩に負けない臨床への寄与ー	秋元哲夫	癌治療増感研究会シンポジウム	2014	国内
前立腺癌に対する放射線療法の進歩	秋元哲夫	前立腺シンポジウム	2014	国内
頭頸部がん治療医の養成の現状と今後の方向について	秋元哲夫	日本頭頸部癌学会	2014	国内
局所進行頭頸部癌に対するセツキシマブ併用放射線治療(BRT)～看護介入による放射線性皮膚炎に対する管理方法の最適化～	石井しのぶ、全田貞幹、秋元哲夫、他	日本放射線腫瘍学会	2014	国内

食道癌に対する化学療法併用陽子線治療の有効性と可能性について	秋元哲夫	日本放射線腫瘍学会	2014	国内
Initial experience of proton beam therapy combined with chemotherapy for locally advanced non-small cell lung cancer and esophageal cancer.	Akimoto T	日本放射線腫瘍学会	2014	国内
当院における骨転移に対する再照射における有害事象の検討	平野博文、中村直樹、秋元哲夫、他	日本放射線腫瘍学会	2014	国内
中咽頭癌に対する強度変調放射線治療の遡及的検討	茂木　厚、全田貞幹、秋元哲夫、他	日本頭頸部癌学会	2014	国内
中咽頭癌におけるがん幹細胞マーカー発現とHPV感染の相関の研究	茂木　厚、林　隆一、秋元哲夫、他	日本放射線腫瘍学会	2014	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文(発表題目)	発表者氏名	発表した場所 (学会誌・雑誌等名)	発表した時期	国内・外の別
Gastrostomy dependence in head and neck carcinoma patient receiving post-operative therapy.	Shinozaki T, Hayashi R Miyazaki M, Tomioka T, Zenda, Tahara T, Akimoto T.	Jpn J Clin Oncol. 44(11) 1058-62	2014	国外
Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up.	Zenda S, Kawashima M, Arahira S, Kohno R, Nishio T, Tahara M, Hayashi R, Akimoto T.	Int J Clin Oncol. in press	2014	国外
Accelerated radiotherapy for T1—T2 glottic cancer.Head and Neck.	Motegi A, Kawashima M, Arahira S, Zenda S, Toshima M, Onozawa M, Hayashi R, Akimoto T.	Head and Neck. in press	2014	国外
Evaluating positional accuracy using megavoltage cone-beam computed tomography for IMRT with head-and-neck cancer.	Motegi K, Kohno R, Ueda T, Shibuya T, Ariji T, Kawashima M, Akimoto T.	J Radiat Res. 55(3) 568-74	2014	国外
Dose calculation accuracies in whole breast radiotherapy treatment planning: a multi-institutional study.	Hatanaka S, Miyabe Y, Tohyama N, Kumazaki Y, Kagami Y, Hiraoka M, Nishio T.	Radiol Phys Technol.	2015	国外
Enhanced radiobiological effects at the distal end of a clinical proton beam: in vitro study.	Matsumoto Y, Matsuura T, Wada M, Egashira Y, Nishio T, Furusawa Y.	J Radiat Res. 55(4) 816-22	2014	国外

IV. 研究成果の刊行物・別刷

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Gastrostomy Dependence in Head and Neck Carcinoma Patient Receiving Post-operative Therapy

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Objective: Post-operative concurrent chemoradiotherapy significantly improves the rates of locoregional control and disease-free survival in high-risk patients but has significant adverse effects. Percutaneous endoscopic gastrostomy and opioid-based pain control increase treatment completion rates but can result in dysphagia.
Methods: The rate and duration of use of prophylactically placed percutaneous endoscopic gastrostomies were evaluated in 43 patients who underwent post-operative radiotherapy or chemoradiotherapy from April 2007 through March 2010. All patients completed treatment and received 60 Gy or more of radiotherapy.
Results: Thirty four of 43 patients (79.1%) used percutaneous endoscopic gastrostomies, which could later be removed in 25 of 34 patients. The median period of use was 108 days. Only one disease-free patient was permanently dependent on percutaneous endoscopic gastrostomy feeding. The frequency of percutaneous endoscopic gastrostomy use among patients with oral, oropharyngeal and hypopharyngeal cancer was 91.7, 100 and 54.5%, respectively.
Conclusions: Prolonged percutaneous endoscopic gastrostomy use is not required in patients receiving post-operative chemoradiotherapy and will not lead to dysphagia.

Key words: post-operative therapy – prophylactic PEG – nutritional management – enteral feeding – H and N-RadOncol – deglutition training

INTRODUCTION

Patients undergoing resection of head and neck cancers with positive surgical margins or extranodal spread of disease are considered to be at high risk for recurrence. Concurrent post-operative chemoradiotherapy for such patients significantly improves the rates of local and regional control and prolongs disease-free survival. However, chemoradiotherapy is associated with a substantial increase in adverse effects (1,2).

Patients with head and neck cancer receiving radiotherapy or chemoradiotherapy are at a considerable risk of malnutrition, with 75–80% of patients experiencing a weight loss during treatment (3–6) of up to 15 or 20% (7,8). Radiotherapy-related toxicities include painful mucositis, dysgeusia, xerostomia, odynophagia, thickened secretions and anorexia (7,9–14). Treatment can, therefore, decrease oral intake by physical means and by decreasing a patient's motivation to eat.

Enteral feeding refers to the delivery of nutrients directly into the stomach via a feeding tube device, such as a nasogastric feeding tube or a gastrostomy tube (15). Enteral tube feeding is used for patients who cannot obtain adequate oral intake of nutrients from food or oral nutritional supplements

or both or who cannot eat or drink safely (16). Enteral feeding can also be used during and after treatment to provide nutritional support to patients with head and neck cancers who are unable to meet their nutritional requirements because of treatment-related side effects.

In our hospital, patients receiving post-operative chemoradiotherapy undergo prophylactic percutaneous endoscopic gastrostomy (PEG). With PEG tube feeding and opioid-based pain control, the completion rate of chemoradiotherapy is increased (17).

Prophylactic PEG has been shown to significantly reduce both mean weight loss and rate of hospitalization during radiotherapy (18–21) and to result in fewer unscheduled treatment interruptions (22). Therefore, in the present study, we examined the rate and duration of use of prophylactically placed PEGs for enteral feeding during post-operative radiotherapy or chemoradiotherapy among patients with head and neck cancers.

PATIENTS AND METHODS

A chart review was performed. We evaluated the rate and duration of use of prophylactically placed PEG tubes for enteral feeding in 43 patients who underwent post-operative radiotherapy or chemoradiotherapy from April 2007 through March 2010 at the National Cancer Research Center East Hospital. Age, sex, location and stage of cancer, extent of surgery and reconstruction, radiation, chemotherapy, use of PEG and removal of PEG were evaluated.

The patients were 31 men and 12 women with a mean age of 57.4 years (range: 26–74 years). All patients completed treatment with 60 Gy or more of radiotherapy and underwent chemotherapy with cisplatin, alone or with fluorouracil or with carboplatin alone. (Table 1) All patients underwent radiation therapy within 8 weeks after definitive surgery consisting of conventionally fractionated doses of 2 Gy in 5 weekly sessions. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of >40–46 Gy. Regions that were adjacent to the high-risk area received a dose of >50–60 Gy. Regions that were at high risk for malignant dissemination or that had inadequate resection margins received a total of 66 Gy in 33 fractions over a period of 6.5 weeks.

Two patients had difficulty with oral ingestion even before radiotherapy.

RESULTS

Prophylactic PEG tubes were used for enteral feeding in 34 (79.1%) of 43 patients and were not used in 9 patients. The PEG tubes that were used were later removed in 25 of the 34 patients (73.5%). The median period of use was 108 days. Among disease-free patients, the rate of feeding tube use was 34.1% (14 of 41 patients) at 6 months, 26.3% (10 of 38 patients) at 1 year, 21.6% at 18 months (8 of 37 patients) and 18.9% (7 of 37 patients) at 2 years. Because of cancer recurrence, eight patients

Table 1. Patients

Male	31	
Female	12	
Age		
Mean, 57.4 years (range: 26–74 years)		
26–59 years	24	
≥60 years	19	
Follow-up		
Alive	24	951–2096 days (median: 1437 days)
Dead	19	132–1098 days (median: 470 days)
Primary site		
Oral cavity	24	
Hypopharynx	11	
Oropharynx	5	
Larynx	3	
T stage		
T1	4	
T2	16	
T3	9	
T4	14	
N stage		
N0	15	
N1	4	
N2	22	
N3	2	
Surgery		
Oral cancer		
Oral cavity resection without reconstruction	10	
Oral cavity resection with reconstruction	9	
Segmental mandibulectomy with reconstruction	5	
Laryngeal/hypopharyngeal cancer		
Total pharyngolaryngoesophagectomy with jejunum reconstruction	8	
Partial laryngectomy/pharyngectomy without reconstruction	6	
Oropharyngeal cancer		
Oropharynx resection without reconstruction	2	
Oropharynx resection with reconstruction	3	
Radiotherapy		
66 Gy	40	
70 Gy	3	
Chemotherapy		
Cisplatin	36	
Cisplatin + fluorouracil	2	
Carboplatin	1	
None	4	

Table 2. Rate and duration of PEG use

Tumor site	Patients	PEG not used	PEG used and removed	Alive with PEG	Used until death	Median duration of use (range), days	Rate of PEG use (%)
Oral cavity	24	2	14	1	7	96 (16–1785)	91.7
Hypopharynx	11	5	5	0	1	93 (20–731)	54.5
Oropharynx	5	0	5	0	0	55 (41–1379)	100
Larynx	3	2	1	0	0	331	33.3
Total	43	9	25	1	8	108 (16–1785)	79.1

PEG, percutaneous endoscopic gastrostomy.

Table 3. Result of analysis with PEG feeding dependence at 1 year

	Oral feeding	PEG use	Rate of PEG tube use at 1 year	
Primary site				
Oral cavity	13	6	31.6% (6 of 19)	
Larynx/hypopharynx/ oropharynx	16	3	15.8% (3 of 19)	$P = 0.445$
Surgery				
Without reconstruction	13	3	18.8% (3 of 16)	
With reconstruction	17	6	26.1% (6 of 23)	$P = 0.882$
Chemotherapy				
Concurrent chemoradiotherapy	27	9	25.0% (9 of 36)	
Radiotherapy alone	2	0	0% (0 of 2)	$P = 0.964$
Age				
<59 years	20	2	9.1% (2 of 22)	
≥60 years	9	7	43.6% (7 of 16)	$P = 0.036$*

* χ^2 test < 0.05.

used PEG tubes until their deaths. One patient, who could not ingest orally before radiotherapy because of dysphagia due to resection of the vagus and hypoglossal nerves, remains alive with a PEG tube. Only one disease-free patient was permanently dependent on PEG feeding.

The rate and duration of PEG use by disease location are shown in Table 2. The PEG was used for feeding in most patients with oral cancer (91.7%) or oropharyngeal cancer (100%) but was used at a much lower rate in patients with hypopharyngeal cancers (54.5%), particularly in those who had undergone pharyngolaryngoesophagectomy. Age >60 years was a factor predicting feeding tube dependence 1 year after (chemo-) radiotherapy (Table 3).

DISCUSSION

Nutritional management is extremely important for the completion of treatment for head and neck cancer. Although the optimal method of nutritional management has been debated, the guidelines of the American Society for Parenteral and Enteral Nutrition state that enteral nutrition is more effective than parenteral nutrition and can be used to optimally maintain the patient's general condition.

In patients receiving chemoradiotherapy for head and neck cancer, hypoalimentation can be caused by numerous complications, including nausea due to chemotherapy, opportunistic infections due to myelotoxicity, mucositis due to radiotherapy or chemotherapy and pain from eczema. Hypoalimentation leads to weight loss and deterioration of the patient's general condition, which, in turn, can lead to a cessation or reduction of treatment, extended hospitalization and a reduced quality of life. For patients with head and neck cancer, PEG is a safe and well-established procedure for delivering nutrition and drugs. On the other hand, a patient's dependence upon PEG for nutrition can lead to a subsequent inability to ingest nutrition orally. Studies, such as those by Mekhail et al. (23) and Baredes et al. (24), have found delays in the resumption of oral ingestion in patients with PEG.

Further retrospective studies have found significantly lower rates of persistent dysphagia 3 and 6 months after surgery in patients fed with nasogastric tubes than in patients fed with PEG tubes (23).

Patients who undergo nasogastric feeding have their feeding tubes removed earlier than do patients who undergo PEG feeding (23,25,26). This notion is supported by the work of Baredes et al. (24), who have reported that PEG tube use leads to a longer period of non-oral feeding because of the deconditioning of the muscles of deglutition. A PEG may also produce feeding tube dependence in patients with dysphagia (27). Kiyota et al. (28) have reported that among patients receiving adjuvant chemoradiotherapy, rates of feeding tube use at 3 months, 6 months and 1 year were 48, 40 and 20%, respectively.

In the present study, the median period of PEG use was 108 days, the rate of use at 2 years was 18.9% and only one patient was permanently dependent on PEG feeding; we consider these results to be satisfactory.

As a result of rehabilitation, there was no statistically significant difference in the rate of feeding tube use 1 year after (chemo-) radiation by primary site, reconstruction or concurrent chemotherapy.

The rate of PEG dependence after 1 year was higher in patients older than 60 years. Therefore, elderly patients have a greater need for rehabilitation than do younger patients.

PEG tubes were used by most patients with oral or oropharyngeal cancers (91.7 and 100%, respectively). On the other hand, the frequency of PEG use was much lower in patients with hypopharyngeal cancer (54.5%), particularly in patients who had undergone pharyngolaryngoesophagectomy. We speculate that a reason for this low rate of PEG use in patients with hypopharyngeal cancer is that areas of radiotherapy-induced mucositis are replaced with free jejunal grafts; because these grafts are poorly sensate, the patients feel little pain, and because the esophagus and respiratory tract are separated to prevent aspiration, oral feeding is relatively easy. Thus, we believe that PEG is unnecessary for patients who have undergone pharyngolaryngoesophagectomy.

Deglutition relies on sensory perception and the action of various organs in the head and neck region. Thus, the temporary absence of deglutition could result in functional decline. Patients being treated for head and neck cancer are likely to forgo deglutition due to either pain or lassitude, with patients using PEGs forgoing deglutition more readily and showing greater functional decline than do patients without PEGs. It is, therefore, necessary for patients with PEGs to continue ingestion and deglutition training.

At our institution, we provide the following support for patients and their families to allow early resumption of ingestion and independence from PEGs:

(1) Continuing guidance, in cooperation with a dentist, regarding oral hygiene and dryness, even after the completion of treatment.
(2) Guidance on meals to enhance appetite in cases of dysgeusia and guidance to ensure adequate nutrition intake.
(3) Guidance with regard to feelings of uneasiness after the removal of the PEG.

As a result of this support, nearly three-quarters of our patients could overcome their dependence on PEGs. In the future, we aim to study further adaptations to PEG feeding by improving the support system and accumulating a large number of cases for study.

CONCLUSION

Prolonged PEG use is not required in patients who undergo postoperative chemoradiotherapy and will not lead to dysphagia. Only one of our patients was permanently dependent on PEG feeding. We believe that our results are satisfactory. However, patients with oral or oropharyngeal cancer who are at a high risk for recurrence are more likely to require prophylactic PEG placement to maintain adequate nutritional status.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up

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Background Although several reports have shown that proton beam therapy (PBT) offers promise for patients with skull base cancer, little is known about the frequency of late toxicity in clinical practice when PBT is used for these patients. Here, we conducted a retrospective analysis to clarify the late toxicity profile of PBT in patients with malignancies of the nasal cavity, para-nasal sinuses, or involving the skull base.

Methods Entry to this retrospective study was restricted to patients with (1) malignant tumors of the nasal cavity, para-nasal sinuses, or involving the skull base; (2) definitive or postoperative PBT (>50 GyE) from January 1999 through December 2008; and (3) more than 1 year of follow-up. Late toxicities were graded according to the common terminology criteria for adverse events v4.0 (CTCAE v4.0).

Results From January 1999 through December 2008, 90 patients satisfied all criteria. Median observation period was 57.5 months (range, 12.4–162.7 months), median time to onset of grade 2 or greater late toxicity except cataract was 39.2 months (range, 2.7–99.8 months), and 3 patients had toxicities that occurred more than 5 years after PBT. Grade 3 late toxicities occurred in 17 patients (19 %), with 19 events, and grade 4 late toxicities in 6 patients (7 %), with 6 events (encephalomyelitis infection 2, optic nerve disorder 4).

Conclusions In conclusion, the late toxicity profile of PBT in patients with malignancy involving the nasal cavity, para-nasal sinuses, or skull base malignancy was partly clarified. Because late toxicity can still occur at 5 years after treatment, long-term follow-up is necessary.

Keywords Proton beam therapy · Late toxicity · Follow-up · Head and neck cancer

Introduction

Malignant tumors that arise in the nasal cavity or paranasal sinuses, or which invade the skull base, usually present a difficult clinical problem.

Most cases are treated by craniofacial surgery and postoperative radiotherapy, either singly or in combination [1–5]. Surgical approaches are often complicated by serious functional deformity and the difficulty of complete resection. In these cases, definitive radiotherapy is performed as an alternative treatment, but aggressive irradiation of the intracranial region increases the risk of severe late toxicity [6–8].

The depth–dose distribution of a proton beam, the Bragg curve, is characterized by an entrance region with a slowly increasing dose followed by a sharp increase near the end of the range, the Bragg peak. This improved dose distribution of proton beam therapy is of therapeutic merit in the

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treatment of deeply seated tumors. The difference between three-dimensional (3D)-conventional radiotherapy (RT) and PBT is clear in dose-painting simulation. Dose coverage to target in intensity-modulated radiotherapy (IMRT) is sufficient; however, the low-dose area is much larger than that of PBT [9].

Therefore, PBT may not be inferior to IMRT or 3D-conventional RT in safety.

Although several reports [10–12] have shown that PBT holds promise for patients with skull base cancer, little is known about the frequency of late toxicity in clinical practice using PBT for these patients.

Here, we conducted a retrospective analysis to clarify the late toxicity profile of PBT for the intracranial region with long-term follow-up.

Patients and methods

Patients

Entry to this retrospective study was limited to patients with (1) malignant tumors of the nasal cavity, para-nasal sinuses, and/or involving the skull base; (2) definitive or postoperative PBT (>50 GyE) from January 1999 through December 2008; and (3) more than 1 year of follow-up. Written informed consent to treatment was obtained from all patients before the initiation of treatment.

Pretreatment evaluation

Pretreatment clinical evaluation was performed using magnetic resonance imaging (MRI), cervical, chest, and abdominal computed tomography (CT), or positron emission tomography (PET)-CT. Tumor staging in the present study was based on the sections on the nasal cavity and paranasal sinuses in the TNM classification of the International Union Against Cancer (UICC 7th), regardless of histology type. Radiologic evaluations for staging were jointly reviewed by radiologists, head-and-neck surgeons, and medical oncologists at our institution.

Late toxicity evaluation

Late toxicity evaluation was mainly performed using MRI and routine physical examination every 3 months until 2 years after treatment, and every 6–12 months thereafter.

Final grade of late toxicities was retrospectively graded by a radiation oncologist based on clinical charts and radiologic findings. Time to onset of toxicity grade 2 or greater was defined as from the day of initiation of treatment to the first day of confirmation of late toxicity of grade 2 or greater.

Proton beam therapy

Treatment planning was performed on a three-dimensional (3D)-CT planning system. In this system, the proton beam was generated with a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biological effectiveness was defined as 1.1, based on our preclinical experiments. Proton beam therapy at our institution is conducted using passive irradiation with dual-ring double-scatter methods. Dose distribution is optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined pretreatment with CT, MRI, and PET-CT, either alone or in combination. Clinical target volume (CTV) was defined for each disease individually. The CTV of patients who had cervical lymph node metastases was defined the same as for those without lymph node metastasis, because this study included only patients who did not have lymph node metastasis or had lymph node metastasis near the primary site. No prophylactic nodal RT was done for any of the patients.

Planning target volume (PTV) was basically defined as the CTV plus a 3-mm margin but could be finely adjusted where necessary in consideration of organs at risk.

Beam energy and spread-out Bragg peak were fine tuned such that the PTV was at least covered in a 90 % isodose volume of the prescribed dosage.

The most common regimen was 65 GyE/26 fr (2.5 GyE/fr), and for only 14 mucosal melanoma patients, a 60 GyE/15 fr (4GyE/fr) regimen was adapted at National Cancer Center Hospital East. Dose constraints for organs at risk in 2.5 GyE fractions were as follows (D_{max}): (1) surface of brainstem, 60 GyE; (2) center of brainstem, 50 GyE; (3) optic nerves of the healthy side/chiasm, 54 GyE; and (4) optic lens, 15 GyE. However, we gave priority to sufficient target coverage when the GTV or CTV was located close to or adjacent to critical organs.

Statistical analysis

Patient demographics and pathological and clinical characteristics were described using descriptive statistics, including mean, standard deviation, median, range, and percentage. Univariate analysis was conducted using the log-rank test. Overall survival and progression-free survival time were estimated by the Kaplan–Meier product–limits method using commercially available statistical software (Stat Mate IV; SAS Institute, Cary, NC, USA).

Definition of local control, progression-free survival, and overall survival

Overall survival time was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival