学 会 等 発 表 実 績

委託業務題目「頭頸部腫瘍に対する強度変調放射線治療の確立と標準化のための臨床研究 」
機関名 学校法人近畿大学

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
Radiotherapy with or without concurrent chemotherapy for T1-3 glottic carcinoma: A retrospective analysis. (Oral Presentation)	Takahashi S, Togami T, Mori T, Kishino T, Hoshikawa H, Mori N, Shibata T	第73回日本医学放射線学会総会、横浜	2014年4月	国内
JCOG多施設共同研究におけるGradient法を用いたCredentialing判定基準に関する考察 (口演)	石川正純、峯村俊行、橘英伸、西村恭昌、西尾禎治、成田雄一郎、遠山尚紀、土屋和彦、戸板孝文、石倉 聡	第73回日本医学放射線学会総会、横浜	2014年4月	国内
上咽頭癌に対する強度変調回転照射の短期成績 (口演)	村上祐司、木村智樹、勝田剛、今野伸樹、土井歓子、岡部智行、権丈雅浩、兼安祐子、永田 靖	第73回日本医学放射線学会総会、横浜	2014年4月	国内
頭頸部癌の放射線治療 (口演)	中村聡明	第73回日本医学放射線学会総会、横浜	2014年4月	国内
A phase 3, multicenter, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with 131I-refractory differentiated thyroid cancer (SELECT). (Oral Presentation)	Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI	ASCO2014,Chicago, USA	May, 2014	国外

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
Effects of aprepitant on the pharmacokinetics of controlled-release oral oxycodone in cancer patients. (Oral Presentation)	Fujiwara Y, Toyoda M, Chayahara N, Kiyota N, Shimada T, Imamura Y, Mukohara T, Minami H	ASCO2014,Chicago, USA	May, 2014	国外
当院における下咽頭癌に対する強度変調放射線治療(IMRT)の初期経験 (ポスター)	土屋和彦、安田耕一、鬼丸力也、白土博樹、本間明宏、福田　諭、清水康、秋田弘俊	第38回日本頭頸部癌学会、東京	2014年6月	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 腫瘍内科医の立場から (口演)	清田尚臣	第38回日本頭頸部癌学会、東京	2014年6月	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 (口演)	秋元哲夫	第38回日本頭頸部癌学会、東京	2014年6月	国内
Accelerated versus Conventional Fractionated Radiotherapy for Glottic Cancer of T1-2N0M0 (JCOG 0701): Comparison of acute toxicity of both group. (Oral Presentation)	Kodaira T, Shikama N, Kagami Y , Ishikura S, Hiraoka M, Nakamura K , Mizusawa J, Saito Y, Matsumoto Y, Nishiyama K, Itami J, Ito Y, Akimoto T, Nakata K, Oguchi M, Nishimura Y, Nakagawa K, Nagata Y, Nishimura T, Uno T, Kataoka M, Yorozu A	5th World Congress of IFHNOS and Annual Meeting of the AHNS, NewYork, USA	July, 2014	国外
Aichi Cancer Experience of Chemo-IMRT using Helical tomotherapy for nasopharyngeal carcinoma. (Oral Presentation)	Kodaira T, Yoshida M, Kimura K, Shimizu A, Takehana K, Makita C, Tomita N, Tachibana H	the 2nd annual meeting Taiwan-Japan Conference on the high precision radiation therapy, Taipei, Taiwan	July, 2014	国外

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Adaptive IMRT for head and neck cancer in Japan. (Keynote Speech)	Nishimura Y	the 2nd annual meeting Taiwan-Japan Conference on the high precision radiation therapy, Taipei, Taiwan	July, 2014	国外
Consideration of pass criteria for IMRT credentialing using the Gradient method in multi-institutional clinical trials. (Oral Presentation Award)	Ishikawa M, Minemura T, Tachibana H, Nishimura Y, Nishio T, Narita Y, Tohyama N, Tsuchiya K, Suzuki R, Ishikura S	the 7th Korea-Japan Joint Meeting on Medical Physics, Busan, Korea	Sept, 2014	国外
Stereotactic body radiation therapy for solitary pulmonary nodules detected after resection of primary lung cancer. (Poster)	Takahashi S, Kimura T, Togami T, Shibata T	the 15th Asian Oceanian Congress of Radiology, Kobe	2014年9月	国内
Radiotherapy for Oropharyngeal Cancers. (Oral Presentation)	Nakamura S	the 15th Asian Oceanian Congress of Radiology, Kobe	2014年9月	国内
The relationship between mean lung dose and pulmonary complications after neoadjuvant chemoradiation therapy followed by surgery for lung cancer. (Poster)	Takahashi S, Go T, Yokomise H, Shibata T	the 56th Annual Meeting of the American Society for Radiation Oncology, San Francisco, USA	Sept, 2014	国外
Results Of Neoadjuvant Chemoradiotherapy Followed By Surgery For Locally Advanced Esophageal Squamous Cell Carcinoma. (Poster)	Murakami Y, Imano N, Doi Y, Okabe T, Kenjo M, Kimura T, Hihara J, Nagata Y	the 56th Annual Meeting of the American Society for Radiation Oncology, San Francisco, USA	Sept, 2014	国外
Statistical process control for EPID dosimetry in the quality assurance of IMRT. (Poster)	Matsumoto K, Okumura M, Asai Y, Shimomura K, Tamura M, Nishimura Y	the 56th Annual Meeting of the American Society for Radiation Oncology, San Francisco, USA	Sept, 2014	国外
Clinical Efficacy Of Helical Tomotherapy For Nasopharyngeal Cancer Treated With Definite Concurrent Chemoradiotherapy. (Poster)	Kodaira T, Tachibana H, Tomita N, Makita C, Shimizu A, Takehana K, Fuwa N	the 56th Annual Meeting of the American Society for Radiation Oncology, San Francisco, USA	Sept, 2014	国外

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
Clinical outcome of radiation therapy for esophageal cancer between 2004 and 2008: second survey. (Poster)	Nishimura Y, Jingu K, Itasaka S, Negoro Y, Murakami Y, Karasawa K, Kawaguchi G, Isohashi F, Kobayashi M, Ito Y, Ariga T	the 56th Annual Meeting of the American Society for Radiation Oncology, San Francisco, USA	Sept, 2014	国外
Clinical results of definitive chemoradiation therapy for T4 esophageal cancer. (Poster)	Ishikawa K, Tatebe H, Matsuura T, Tachibana I, Yokokawa M, Nakamatsu K, Kanamori S, Nishimura Y	the 56th Annual Meeting of the American Society for Radiation Oncology, San Francisco, USA	Sept, 2014	国外
頭頸部癌の放射線治療 (口演)	中村聡明	広島大学病院放射線治療講演会、広島	2014年10月	国内
甲状腺がんに対する分子標的薬の適正使用と副作用管理について (口演)	清田尚臣	第47回日本甲状腺外科学会、福岡	2014年10月	国内
進行性甲状腺癌（放射性ヨウ素治療抵抗性の分化癌，髄様癌，未分化癌）に対するレンバチニブの第2相試験 (口演)	清田尚臣	第47回日本甲状腺外科学会、福岡	2014年10月	国内
当院における下咽頭癌に対する強度変調放射線治療（IMRT）の初期経験 (口演)	土屋和彦、安田耕一、原田八重、鬼丸力也、白土博樹	第131回日本医学放射線学会北日本地方会、仙台	2014年10月	国内
中咽頭扁平上皮癌：HPV関連、亜部位別予後比較 (口演)	利安隆史、吉田匡宏、原田亜里咲、大久保裕史、八木緑、宮澤一成、浅利崇生、小塚拓洋、小口正彦	日本放射線腫瘍学会第27回学術大会、横浜	2014年12月	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）(口演)	石井しのぶ、全田貞幹、荒平聡子、茂木厚、秋元哲夫	日本放射線腫瘍学会第27回学術大会、横浜	2014年12月	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 (口演)	茂木　厚、林隆一、全田貞幹、秋元哲夫	日本放射線腫瘍学会第27回学術大会、横浜	2014年12月	国内

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
喉頭･下咽頭癌 機能温存への挑戦 (口演)	中村聡明	日本放射線腫瘍学会第27回学術大会、横浜	2014年12月	国内
頸部食道癌に対する化学放射線療法 (食道がん･口演)	板坂　聡	日本放射線腫瘍学会第27回学術大会、横浜	2014年12月	国内
IVA/IVB期中下咽頭癌に対する導入化学療法後化学放射線治療の初期経験 (口演)	村上祐司、久保克麿、坂口弘美、川畑秀雄、今野伸樹、土井歓子、岡部智行、権丈雅浩、木村智樹、永田　靖	日本放射線腫瘍学会第27回学術大会、横浜	2014年12月	国内
頭頸部癌と食道癌の同時重複癌に対する根治照射の経験 (口演)	髙橋重雄、木下敏史、戸上太郎、柴田　徹	第123回日本医学放射線学会中国･四国地方会、愛媛	2014年12月	国内
Delineating target in head and neck cancer. (Oral Presentation)	Shibata T	IAEA/RCA regional training course: An update on Advanced Technologies in Radiotherapy, Hiroshima	2015年2月	国内
IMRTによる正常組織有害事象の低減 (口演)	柴田　徹	香川県がん診療連携拠点病院研修セミナー、香川	2015年3月	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
Radiation therapy quality assurance in clinical trials--Global Harmonisation Group.	Melidis C, Bosch WR, Izewska J, Fidarova E, Zubizarreta E, Ishikura S, Followill D, Galvin J, Xiao Y, Ebert MA, Kron T, Clark CH, Miles EA, Aird EG, Weber DC, Ulin K, Verellen D, Hurkmans CW	Radiother Oncol. 111(3):327-9	2014年	国外
Definitive radiotherapy for head and neck squamous cell carcinoma; update and perspectives on the basis of EBM.	Kodaira T, Nishimura Y, Kagami Y, Ito Y, Shikama N, Ishikura S, Hiraoka M	Jpn J Clin Oncol. 45(3):235-43(doi: 10.1093/jjco/hyu209)	2014年	国外
Randomized phase II/III trial of postoperative chemoradiotherapy comparing 3-weekly cisplatin with weekly cisplatin in high-risk patients with squamous cell carcinoma of head and neck: Japan Clinical Oncology Group Study (JCOG1008).	Kunieda F, Kiyota N, Tahara M, Kodaira T, Hayashi R, Ishikura S, Mizusawa J, Nakamura K, Fukuda H, Fujii M, and Head and Neck Cancer Study Group of the Japan Clinical Oncology Group	Jpn J Clin Oncol. 44(8):770-4	2014年	国外
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年	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年	国外

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
Adjuvant treatment for post-operative head and neck squamous cell carcinoma.	Kiyota N, Tahara M, Fujii M	Jpn J Clin Oncol. 45(1):2-6	2014年	国外
Longitudinal change in health-related quality of life after intensity-modulated radiation monotherapy for clinically localized prostate cancer.	Yamamoto S, Fujii Y, Masuda H, Urakami S, Saito K, Kozuka T, Oguchi M, Fukui I, Yonese J	Qual Life Res. 23(5):1641-50	2014年	国外
Prognostic biomarkers in patients with localized natural killer/T-cell lymphoma treated with concurrent chemoradiotherapy.	Yamaguchi M, Takata K, Yoshino T, Ishizuka N, Oguchi M, Kobayashi Y, Isobe Y, Ishizawa K, Kubota N, Itoh K, Usui N, Miyazaki K, Wasada I, Nakamura S, Matsuno Y, Oshimi K, Kinoshita T, Tsukasaki K, Tobinai K	Cancer Sci. 105(11):1435-41	2014年	国外
Multimodal treatment for T1-2 supraglottic cancer: the impact of tumor location.	Suzuki G, Yamazaki H, Ogo E, Abe T, Hayabuchi N, Umeno H, Nakashima T, Nakamura S, Yoshida K	Anticancer Res. 34(1):203-7	2014年	国外
TYRO3 as a potential therapeutic target in breast cancer.	Ekyalongo RC, Mukohara T, Funakoshi Y, Tomioka H, Kataoka Y, Shimono Y, Chayahara N, Toyoda M, Kiyota N, Minami H	Anticancer Res. 34(7):3337-45	2014年	国外

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
Predisposing Factors for Larynx Preservation Strategies with Non-surgical Multimodality Treatment for Locally Advanced (T3-4) Larynx, Hypopharynx and Cervical Esophageal Disease.	Suzuki G, Yamazaki H, Ogo E, Abe T, Eto H, Muraki K, Hattori C, Umeno H, Tanaka N, Tanaka T, Nakamura S, Yoshida K	Anticancer Res. 34(9):5205-10	2014年	国外
Hypofractionated Stereotactic Radiotherapy Using CyberKnife as a Boost Treatment for Head and Neck Cancer, a Multi-institutional Survey: Impact of Planning Target Volume.	Yamazaki H, Ogita M, Himei K, Nakamura S, Yoshida K, Kotsuma T, Yamada Y, Fujiwara M, Baek S, Yoshioka Y	Anticancer Res. 34(10):5755-9	2014年	国外
Prognostic Value of FDG PET Imaging in Patients with Laryngeal Cancer.	Kitajima K, Suenaga Y, Kanda T, Miyawaki D, Yoshida K, Ejima Y, Sasaki R, Komatsu H, Saito M, Otsuki N, Nibu K, Kiyota N, Minamikawa T, Sugimura K	PLoS One. 12;9(5):e96999	2014年	国外
Effects of aprepitant on the pharmacokinetics of controlled-release oral oxycodone in cancer patients.	Fujiwara Y, Toyoda M, Chayahara N, Kiyota N, Shimada T, Imamura Y, Mukohara T, Minami H	PLoS One. 14;9(8):e104215	2014年	国外
Clinical results of definitive-dose (50 Gy/25 fractions) preoperative chemo-radiotherapy for unresectable esophageal cancer.	Ishikawa K, Nakamatsu K, Shiraishi O, Yasuda T, Nishimura Y	Int J Clin Oncol. [Epub ahead of print]	2014年	国外

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
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. [Epub ahead of print]	2014年	国外
Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III.	Singer S, Araújo C, Arraras JI, Baumann I, Boehm A, Brokstad Herlofson B, Castro Silva J, Chie WC, Fisher S, Guntinas-Lichius O, Hammerlid E, Elisa Irarrázaval M, Jensen Hjermstad M, Jensen K, Kiyota N, Licitra L, Nicolatou-Galitis O, Pinto M, Santos M, Schmalz C, Sherman AC, Tomaszewska IM, Verdonck de Leeuw I, Yarom N, Zotti P, Hofmeister D	Head Neck. doi: 10.1002/hed.23762. [Epub ahead of print]	2014年	国外
Accelerated hyperfractionated radiotherapy for small-cell carcinoma of the nasopharynx.	Takahashi S, Miyashita T, Hoshikawa H, Haba R, Togami T, Shibata T	Head Neck. [Epub ahead of print]	2014年	国外
悪性リンパ腫に対する放射線治療の新しい動き —ISRTを中心に—	小口正彦、長谷川正俊、石橋直也、磯部公一、今井美智子、江島泰生、糟谷健夫、片山絵美子、笹井啓資、副島俊典、早渕尚文、日本放射線腫瘍学研究機構 悪性リンパ腫・血液腫瘍委員会	臨床血液 55(10):1903-11	2014年	国内

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
頭頸部がん化学療法ハンドブック 第1版	藤井正人、 田原信、 清田尚臣	中外医学社	2014年	国内
Guidelines for diagnosis and treatment of carcinoma of the esophagus April 2012 edited by the Japan Esophageal Society.	Kuwano H, Nishimura Y, Oyama T, Kato H, Kitagawa Y, Kusano M, Shimada H, Takiuchi H, Toh Y, Doki Y, Naomoto Y, Matsubara H, Miyazaki T, Muto M, Yanagisawa A	Esophagus. 12:1-30	2015年	国外
Lenvatinib versus placebo in radioiodine-refractory thyroid cancer.	Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI	N Engl J Med. 12;372(7):621-30	2015年	国外
当院における再発・転移頭頸部がんに対するドセタキセル・シスプラチン併用療法の遡及的解析	島田 貴信、清田 尚臣、今村 善宣、森本 浩一、斉藤 幹、西村 英輝、大月 直樹、佐々木 良平、丹生 健一	頭頸部癌 40(4):490-6	2015年	国内

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Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Editorial

Radiation therapy quality assurance in clinical trials – Global harmonisation group

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Participation in large multi-centre clinical trials aids establishment of the safety and efficacy of new cancer treatments and methods. Oncology clinical trials have contributed to improved local control, overall survival and quality of life for patients with varying disease types [1]. Radiation Therapy is indicated in the course of treatment for more than 50% of all cancer patients [2,3] and consequently a high percentage of oncology clinical trials include radiotherapy within their treatment schema.

Collaboration between global clinical trial groups and organisations has increased the number of patient records available for analysis permitting faster recruitment [4], broader acceptance and wider impact of trial results. Global cooperation is also essential in the environment of rare cancers [5], in order to be able to create sufficiently large patient data sets within a reasonable recruitment period. A successful example is the EORTC 26981/National Cancer Institute of Canada (NCIC) CE3 intergroup trial, where 573 Glioblastoma patients were randomised within 20 months [6], despite the low prevalence of the disease among the general population.

Globally, clinical trial groups and organisations have independently implemented their own Radiation Therapy (RT) Quality Assurance (QA) programs within their corresponding large multi-centre clinical trials. Various trial groups have reported that the implementation of RTQA procedures enhanced protocol compliance [7–13]. In four Radiation Therapy Oncology Group (RTOG) studies compliance with the study protocol was enhanced by incorporating pre-treatment review of RT planning [8]. A Trans-Tasman Radiation Oncology Group (TROG) QA audit identified a reduction in unacceptable protocol violations due to three main factors, among which was the QA procedure itself [7]. More recently, strict RTQA procedures have been shown by TROG to have impacted on both trial protocol compliance as well as general clinical practice in prostate RT [9]. For several EORTC studies it has been shown that centres which previously participated in a Dummy Run (DR) were significantly more likely to be successful at subsequent DR attempts and delivery of protocol-compliant RT [10]. Additionally, the impact of RTQA on actual clinical trial outcome has been recently demonstrated in the setting of various cancer sites [11], stressing its importance and correlation with survival [12,13].

However, the various approaches as to how RTQA in clinical trials is performed, evaluated and described are diverse, making analysis and inter-trial comparisons of RTQA results challenging. This hampers cooperation between trial groups and impedes the exchange and interpretation of RTQA data. The costs of running an RTQA program have also increased with the introduction of new advanced technologies. This increases the need to make RTQA more efficient and streamline the QA workload demanded of clinical centres recruiting into international trials [14,15]. As shown by Pettersen et al [4] these RTQA efforts can potentially reduce the number of patients required for trials which could lead to further substantial savings and faster availability of results.

The need for a global forum on harmonisation of RTQA within clinical trials thus became apparent. After initial discussions in Göteborg during ESTRO 27 in 2008 the Global Clinical Trials RTQA Harmonisation Group (GHG) was formally established in 2010.

The goals of the GHG are:

(1) Collate, homogenise and distribute information regarding the RTQA standards of the clinical trial groups,
(2) Provide a platform for prospective discussions on new RTQA procedures, software tools, guidelines and policies of trial groups and
(3) Provide a framework to endorse existing and future RTQA procedures and guidelines across various trial groups.

Each organisation will have the opportunity to endorse RTQA procedures from other organisations and thus accept them much faster in future collaborative trials.

In Table 1 the human resources and number of intergroup trials of the steering committee members of the GHG are given. Further information about terms of reference and current and future projects can be found on its website: www.RTQAHarmonisation.org.

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http://dx.doi.org/10.1016/j.radonc.2014.03.023

Table 1
RTQA within each of the current GHG steering committee members as of August 2013.

GHG member	Year of RTQA implementation	Current human resources	Current number of intergroup trials and RTQA projects
EORTC–ROG	1982	Full time: 1 radiation oncologist, 1 medical physicist, 1 radiation technologist In kind: ROG members	9
IAEA	1969	Full time: 4 radiation oncologists, 3 medical physicists, 1 lab technician, administrative support, an individual data management centre per trial In kind: 1 Medical Physicist	11
ITC	1994	Full time: 2 medical physicists, 2 informaticists, 3 data managers	45
JCOG	1999	In kind: 18 radiation oncologists, 12 medical physicists	5
RTTQA	1987	Full time: 1 radiation oncologist, 3 medical physicists, 3 radiation technologists Part-time: 1 radiation oncologist, 17 medical physicists, 3 radiation technologists, 1 dosimetrist, 2 IT support, 1 administrative support In kind: 3 medical physicists	6
QARC	1980	Full-time:1.5 Radiation Oncologists, 0.5 Medical Physicist, 4.1 Research Dosimetrists, 4 Informatics Support Personnel, 9.5 Data Managers, 3 Administrative Support Personnel.	54
RPC	1968	Full time: 7 medical physicists, 3.5 research dosimetrists, 3 IT support, 6 administrative support employees, 5 optically-stimulated/thermoluminescent dosimeter technicians, 4 physicist assistants, 0.5 machinist	50
RTOG	1968	Full time: 2 medical physicists, 5 dosimetrists, 1 data assistant & credentialing, 1 administrative support	67
TROG	1989	Full time: 1 manager, 1 radiation therapist, 0.4 medical physicist, 1 research officer, 0.5 IT support. For software support: 1 programmer, 1 physicist In kind: TROG members	9

All RTQA groups and organisations participate in international collaborative work to some degree, although there are differences between the USA and all other groups. These differences can be explained by the differences in the funding levels and that most USA RTQA groups only work with NCI funded clinical trials mainly operated in North America [16]. Recently, the North American RTQA organisations have joined forces in the new Imaging and Radiation Oncology Core (IROC) group. The dedicated human resources also vary significantly, most likely due to differences in the QA philosophy of the funding agencies and their commitment to RTQA, although most of the GHG members have at least one Radiation Oncologist, one Medical Physicist and one Radiation Technologist dedicated full time to RTQA.

Until now the GHG has contributed to the harmonisation of naming conventions [17], strategies to develop an efficient evidence-based clinical trials RTQA system [14] and the development of a global model for the international recognition of the activities of national and regional Dosimetry Audit Networks [18]. Currently, each trial group has defined its own RTQA procedures [10,19–24] that differ significantly in number, naming conventions and implementation methods [22,25–31]. The GHG is addressing this by collating all RTQA procedures of each member, comparing them and proposing common, harmonised names and procedures.

Although RTQA has been proven to be effective, international differences hamper intergroup collaboration. The Global Clinical Trials RTQA Harmonisation Group has been established to reduce those differences, capitalise on the range of expertise available internationally, increase the power of RT clinical trials, deliver consistency in the reporting of trial quality factors and facilitate the undertaking of effective multi-national trials and data analysis. Although important progress has already been made, many challenges remain to be addressed.

Conflict of interest statement

None declared.

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Japanese Journal of Clinical Oncology Advance Access published December 9, 2014

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2014, 1–9
doi: 10.1093/jjco/hyu209
Review Article

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Review Article

Definitive radiotherapy for head and neck squamous cell carcinoma: update and perspectives on the basis of EBM

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Received 29 October 2014; Accepted 19 November 2014

Abstract

Radiotherapy plays an essential role in the management of head and neck squamous cell carcinoma. Radiotherapy has a distinct advantage over surgical procedures in that it could achieve organ and function preservation with an efficacy similar to that of surgical series. To improve the clinical outcomes achievable by radiotherapy, altered fractionated radiotherapy has been prospectively tested for early and intermediate risk diseases, and was previously shown to be beneficial for local control and survival. Radiotherapy alone is insufficient for locally advanced disease; therefore, concurrent chemoradiotherapy is typically performed and plays an important role. A meta-analysis (Level Ia) revealed that the concurrent use of platinum agents appeared to improve tumor control and survival; however, this was accompanied by increases in the rates of both acute and late toxicities. Regarding radiation techniques, intensity modulated radiotherapy evolved in the 1990s, and has been globally used to treat head and neck squamous cell carcinoma patients. Intensity modulated radiotherapy reduces the exposure of normal tissue to radiation while preserving excellent dose coverage to the target volume; therefore, the rate of late toxicities especially xerostomia is minimized. Small size randomized studies and a meta-analysis have provided evidence to support the benefits of intensity modulated radiotherapy over two-dimensional or three-dimensional radiation therapy. Intensity modulated radiotherapy can also preserve quality of life following definitive chemoradiotherapy. Further improvements using intensity modulated proton therapy are warranted.

Key words: intensity modulated radiotherapy, chemoradiotherapy, altered fractionated radiotherapy

Introduction

Radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC) plays an important role in the preservation of organs and their functions. Small volume tumors, such as those of the T1–2 category, are expected to achieve 70–90% local control with RT (1–4); however, the efficacy of RT alone was shown to be reduced in cases of T3–4 category tumors (5–7). Controversy still surrounds the ability of RT to achieve tumor control and larynx preservation in locally advanced laryngeal and hypopharyngeal cancers. Although concurrent chemoradiotherapy (CCRT) appears to be the mainstay for successful

larynx preservation compared with surgery, increases in late morbidity and controversy in survival benefit with a longer follow-up are serious issues(8,9). Intensity modulated radiotherapy (IMRT) has rapidly evolved in the past two decades, and is considered the standard care of definitive RT for HNSCC (10). Previous studies reported that the rate of late morbidities especially xerostomia appeared to be lower following IMRT (11–16), and improved quality of life (QOL) after RT could be expected (17–20). Thus, the adaptation of IMRT for CCRT represents a reasonable combination to minimize the risk of the associated toxicities. Multi-agent induction chemotherapy containing taxanes and bioradiotherapy has been extensively researched in an attempt to balance treatment efficacy and safety (21–23).

Early stage

Optimal fractionation schedule

Prolonging the duration of RT for HNSCC is known to have a distinct negative impact on clinical outcomes (24–26), and has been attributed to a biological phenomenon, the so-called accelerated repopulation, which is accompanied by the development of radioresistance by tumor cells (27). To improve clinical outcomes, an altered fractionation (AF) schedule that minimizes the treatment duration, has been clinically tested on patients with low and intermediate risk diseases (28–31). A meta-analysis revealed that AF improved both local control and survival over those achieved by the standard fractionated schedule (32).

Early glottis cancer is considered to be an optimal model for presenting the advantages of AF. Definitive RT was previously reported to have acquired sufficient survival outcomes with excellent local control for patients with this cancer, even if salvage surgery for local recurrence was needed. Patients with T1–2N0 glottic cancer typically receive 66–70 Gy over 6.5 weeks on an outpatient basis. AF is expected to improve tumor control, thereby reducing the burden on patients and working staff, and ameliorating the cost of treatment for public insurance. Several retrospective studies have demonstrated the advantages of AF radiotherapy (>2.0 Gy per fraction) for glottis cancer (33,34); however, few prospective studies have been conducted in a multi-institutional setting (Table 1) (29–31). Yamazaki et al. (29) reported that the AF arm in a randomized controlled study from a single institute showed a significant advantage for local control. A total of 180 patients with T1 glottic tumors were entered into this trial; the AF arm ($N = 91$) received 56.25–63 Gy over 5–5.5 weeks with a 2.25 Gy fraction, while the SF arm received 60–66 Gy over 6–6.5 weeks with a 2 Gy fraction. The 5-year local control rate of the AF arm was significantly better than that of the standard fractionation (SF) arm (92 vs. 77% $P = 0.004$). Moon et al. (30) reported the findings of multi-institutional randomized controlled trial (RCT) for T1–2N0M0 glottic cancer. However, this trial was stopped due to poor accrual, because only 156 patients were ultimately registered against the planned 282 patients. The AF arm of 63–67.5 Gy with a 2.25 Gy fraction achieved slightly better local control than that of the SF arm of 66–70 Gy with a 2 Gy (93 vs. 76%; $P = 0.056$). The Radiation Therapy Study Group of the Japan Clinical Oncology Group (JCOG) conducted a multi-institutional RCT trial of the JCOG 0701 to demonstrate the non-inferiority of the efficacy of the AF arm with 2.4 Gy per fraction over the SF arm with 2 Gy per fraction (31). A total of 370 patients were registered in this study until January 2013, and a follow-up will be conducted on January 2016. It is the first multi-institutional RCT trial to investigate the advantage of AF radiotherapy for early glottic cancer, the findings of which are highly anticipated.

Intensity modulated radiotherapy

The incidence of oropharyngeal cancer (OPC) is gradually increasing, while that of human papilloma virus (HPV) infection is also high (35,36). Patients with OPC-related HPV infection have a favorable prognosis (37–39), and radiotherapy plays an important role among the treatment modalities available for these patients. The adaptation of IMRT could reduce the rate of late toxicity especially xerostomia; thus, it is considered a standard method in definitive RT for OPC (40,41). Several RCT have been conducted to demonstrate the advantages of IMRT for HNSCC patients including OPC (11,13). The RTOG 00-22 trial is a prospective single arm trial that tested the efficacy of IMRT using a slightly hypofractionated schedule with 2.2 Gy per fraction for early OPC patients with T1–2N0–1M0 diseases (42). The 2-year survival rate was reported to be 95.5%, with a loco-regional failure rate of only 9%. The 1- and 2-year rates of Grade 2 xerostomia were 25 and 16%, respectively. To further improve QOL, unilateral neck irradiation using IMRT for OPC, with a favorable prognostic factor, is expected to represent an attractive treatment option (43). Al-Mamgani et al. (44) retrospectively evaluated unilateral neck IMRT for early disease in this category in a relatively large series ($N = 185$). The 5-year local control rate was reported to be 91% with 7% Grade 2 xerostomia. Although this was a retrospective

Table 1. Reported series of definitive radiotherapy with altered fractionation for early glottic cancer

Author	Material	Number	Style	Total dose (Gy)	Fraction size (Gy)	LC (%)	OS (%)	Complication rate G3 or more
Robertson (33)	T1–4	118	Retrospective	60	2	55–70/39–62	NR	NR
		15		56.5	2.26	80/	NR	NR
		111		60	2.4	95/75	NR	NR
		37		54	3	81/37	NR	NR
		22		51	3.4	85/40	NR	NR
van der Voet (34)	T1	64	Retrospective	60–66	2	83–85		NR
		79		60, 61.6	2.4, 2.8	90–93		1.8–3.1
		142		62, 65	3.1, 3.25	93		10.9–12.5
Mendenhall (1)	T1–2	304	Retrospective	56.25/63 (T1/2)	2.25	93/75	NR	1.6
Yamazaki (29)	T1	180	Prospective Phase III	56.25/63 (S/L)	2.25	92	87	0
Moon (30)	T1–2	156	Prospective Phase III		2.25	88.5(LPFS)	86.6	0
RTOG 9512 (28)	T2	250	Prospective Phase III	79.6	1.2 bid	78	72	8.5
JCOG 0701 (31)	T1–2	370	Prospective Phase III	60/64.8 (T1/T2)	2.4			

S, small size; L, large size, bid, twice-a-day, LC, local control; LPFS, larynx progression-free survival; OS, overall survival; NR, not reported.

study, limited field IMRT was expected to successfully achieve high local control with a low incidence of xerostomia. The JCOG Radiation Therapy Study Group has now conducted the JCOG 1208 study to test the efficacy of IMRT using a limited target volume (TV) for patients with OPC of the T1–2N0–1 category. In this protocol, contralateral Level II–III area was excluded from prophylactic TV in the case of patients with tonsillar cancer. And only ipsilateral Level IV area was included in TV for patients with N1. This is the first multi-institutional prospective trial using this modified TV for early OPC.

Locally advanced stage

The efficacy of RT alone for locally advanced (LA) disease is lower than that of surgical series. The administration of cytotoxic agents to improve disease control has been practically considered for patients with certain medical conditions (5,23,45–47). CCRT was reported to significantly improve both disease control and survival in several RCTs, and these findings were also supported by meta-analyses (5,45,46,48). RT accompanied with platinum agents is considered the standard treatment for LA-HNSCC (45).

RT with cetuximab [CET; anti-epidermal growth factor receptor (EGFR)] also improved overall survival (OS) and LC over those with RT alone (47,49). In the Bonner trial, Stage III–IV patients were randomly assigned to a bioradiotherapy (BRT) arm or RT arm. The BRT arm showed significant improvements in loco-regional control and OS [hazard ratio (HR) 0.68; $P = 0.005$; HR = 0.74 $P = 0.03$]. No significant difference was observed in the rate of acute toxicities between both arms. Therefore, it is important to note that a direct comparison has not yet been conducted between the results achieved by BRT and CCRT, which is considered the standard treatment for LA-HNSCC (50).

AF has also been shown to increase local control for LA-HNSCC in several RCTs. A meta-analysis of 15 trials with 6515 patients revealed that AF was significantly advantageous for local control and OS (Level Ia) (32). The majority of cohorts were comprised of OPC patients (47.2%) and Stage III patients, who were expected to have relatively good prognoses, and these groups had slightly better OS in the subset analysis.

Although both chemical modulations by CCRT or BRT and dose modifications by AF increase tumor control, they are also accompanied by increased rates of acute and late toxicities due to definitive RT. The adaptation of IMRT should minimize the rates of these toxicities and, as such, is highly recommend for use in an intensive strategy for LA-HNSCC (13,16,20).

Optimal method of chemotherapy

The standard treatment for locally advanced HNSCC still remains concurrent chemoradiotherapy (CCRT) with cisplatin (45). Previous studies reported Level Ia evidence for the efficacy of CCRT (46,48).

MACH-NC trial comprised 93 trials with 17 346 patients, conducted between 1965 and 2000, revealed that the efficacy of CCRT was higher than that of induction or adjuvant chemotherapy (46). The administration of chemotherapy showed a 4.5% absolute benefit in survival and reduced the HR by 12% ($P < 0.0001$). Regarding the timing of chemotherapy, CCRT achieved a 6.5% absolute benefit in 5-year OS, and a 19% reduction in the HR of OS. In that study, induction chemotherapy (IC) led to moderate benefits in OS and had an apparent advantage by decreasing the rate of distant metastasis (46). This study also showed the benefits of CCRT were less in elderly patients ($P = 0.003$).

IC with taxanes containing multi-agents (ITM) was recently reported to be more advantageous for OS and disease control than cisplatin and 5-FU (PF) in RCTs (21,22), and these findings were confirmed by a meta-analysis (23). Several RCTs were previously conducted to compare the efficacy of ITM to that of PF; however, its apparent benefits over that of immediate CCRT have not been reported until now (51–53). One of the weaknesses of the ITM strategy was the significant increase in treatment-induced toxicities, which decreased compliance of following CCRT (54). Approximately half of the ITM cohorts could not receive chemotherapy during radiotherapy (21,22), which may have decreased the efficacy of CCRT. Several studies attempted to test ITM followed by BRT (55,56). In the Bonner trial, RT with CET was reported to induce similar acute toxicities to those of RT alone (49). ITM followed by BRT represents an attractive strategy for managing treatment toxicities without sacrificing efficacy. Ghi et al. (56) performed a randomized Phase II/III trial to test the efficacy of adding IC containing docetaxel, cisplatin and 5-FU. This trial had a 2 × 2 factorial design, in which second randomization of the CCRT arm or BRT arm occurred after first randomization of IC. They reported survival benefits in the ITM arm. Further modifications and optimization are required to balance the efficacies and morbidities of such intensive multidisciplinary treatments.

Role of bioradiotherapy

The Bonner trial reported the significant advantage of BRT toward RT alone in RCT with LA-HNSCC patients (47,49). Only one RCT has demonstrated the benefit of BRT; however, the control arm in this RCT was RT alone, which is not considered a standard treatment for LA-HNSCC. One of the expected merits of BRT is reduced toxicity. In the Bonner trial, acute toxicities were similar between the BRT arm and RT arm. Several randomized Phase II studies compared BRT with CCRT (55,56). The TREMPLIN trial was conducted to test larynx preservation rate of BRT compared with CCRT for patients treated with ITM for LA-HNSCC (55). Local control could not be achieved by 12 patients (21%) in the BRT arm and eight patients (13%) in the CCRT arm; however, this difference was not significant. BRT was shown to have superior compliance over CCRT (71 vs. 43%), and salvage surgery could be performed in six out of nine patients assessed as feasible for surgery in the BRT arm, but in none of the eight patients in the CCRT arm. Consequently, OS rates were similar in both arms. Ghi et al. (56) also conducted a Phase II/III study of randomization of BRT and CCRT arms. This trial also determined the efficacy of ITM with a 2 × 2 factorial design. No significant differences were observed in progression-free survival (PFS) or OS rates between the BRT and CCRT arms.

A systemic review was conducted on 15 trials comprising 1808 patients to compare BRT and CCRT (50). Only three trials were prospective, while the other 12 were retrospective. In this systemic review, CCRT achieved significantly better OS, PFS and LRR than BRT. RTOG 1016, a Phase III trial of BRT versus CCRT for HPV-associated OPC, is currently being conducted (57). This is the first trial to directly compare BRT and CCRT for a favorable risk group. The effectiveness and toxicity of BRT may be demonstrated in this trial, and its findings could also resolve the question as to whether the efficacy of BRT is similar to that of CCRT.

RTOG 0522 trial was designed to compare the CCRT with cetuximab (CET) arm to the CCRT arm (58). The 3-year OS, PFS and loco-regional relapse-free rate (LRF) were similar in both arms; however, the incidence of acute adverse events was higher in the combined arm. These findings suggest that CCRT with anti-EGFR should be tested in clinical trials, and special care should be taken for its clinical use.

To minimize the toxicity of definitive intensive RT, dose reductions using BRT for a favorable group is now being prospectively evaluated

(59). HPV-associated OPC patients are the main target in this trial. Reductions in toxicity are warranted after confirmation of its efficacy in the de-escalation trial.

Larynx preservation

Locally advanced laryngeal (LC) and hypopharyngeal cancers (HPC) have been treated with surgery, while laryngeal preservation (LP) with the aim of preserving the voice and swallowing function without sacrificing survival is considered a reasonable option in clinical practice (Table 2) (5–7,22,60–62). In the 1990s, several RCTs demonstrated the feasibility of the LP strategy (5–7,62,63). Two RCTs compared IC followed by RT with immediate surgery, the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) trial for LC (7) and EORTC 24851 trial for HPC (6). The VALCSG study registered 322 patients with Stage III/IVLC. The IC group received two cycles of 5FU and cisplatin, then responders to chemotherapy were treated with definitive RT. Otherwise patients underwent laryngectomy with or without post-operative RT. In the IC arm, 107 patients (64%) preserved their larynx. The 2-year OS rate of both groups was 68%. In a subgroup analysis, 56% of patients with T4 category tumors and 29% of those with smaller lesions required salvage surgery. In the EORTC 24851 study, 194 patients with T2–4, N0–2b LA-HPC were randomized to an IC arm or immediate surgery arm (6). The DFS rates at 3 and 5 years were 43%/25% for the IC arm and 32%/27% for the surgery arm, respectively. The 3- and 5-year functional LP rates were 64 and 58% for patients with completed treatments from the IC arms. Responses to the LP protocol markedly varied according to the T category (T2 for 82%, T3 for 48% and T4 for 0%). In these two studies, approximately two-thirds of the IC group could preserve the larynxes without sacrificing survival against the surgical series.

RTOG 91-11 study was a RCT conducted to demonstrate the efficacy of three different RT arms including RT alone, IC followed by RT (identical to the VALCSG trial) and CCRT (5,62). A total of 547 patients with Stage III/IV LC were registered in this trial. Its findings were initially reported in 2003 (5), and then updated in 2012 (62). The rates of LP at a median follow-up of 3.8 years and 10.8 years were 83.6 and 81.7% for the CCRT arm, respectively, and were significantly higher than those from the other two arms (70.8 and 67.5% for the IC arm and 65.8 and 63.8% for the RT alone arm). The OS rates at 5 and 10 years did not differ among the treatment groups (55 and 27.5% for the CCRT arm, 59 and 39% for the IC arm and 54 and 31.5% for the RT alone arm). Although failure to achieve local control was lower in the CCRT arm, the rate of toxicity would have considerably increased with a longer follow-up. In this update series, the CCRT arm had better disease control and a higher rate of late toxicity. From the viewpoint of LP, ITM is expected to allow for feasible options, balancing its efficacy and lower toxicity. A multi-institutional consensus panel published guidelines for the conduct of RCTs for LP (64). They recommended the enrollment of patients with T2 or T3 LC or HPC. They also emphasized that clinical and instrumental assessments were essential, and also proposed the endpoint of disease free with a functional larynx, such as *laryngo-esophageal dysfunction-free survival*. Minimum invasive surgery has recently evolved, and objective and functional estimations are needed for comparisons between different treatment modalities including surgical series (60,65).

Role of intensity modulated radiotherapy

The use of IMRT has recently become more widespread, and this modality was supported by novel technological developments in the 1990s (10). Using this technique, conformal dose distributions to the clinical target volume could be achieved with identical dose reductions to the surrounding normal tissue. Several RCTs demonstrated that IMRT could reduce the rate of G2 xerostomia below that of the 2D or 3D technique (Table 3) (11–16). Two East-Asian RCTs were conducted using a small cohort ($N = 45$–56) of early nasopharyngeal

Table 2. Larynx preservation trials using induction chemotherapy for laryngeal and hypopharyngeal cancer

Study	Number	Site	Stage	IC	RT	LP (%)	OS (%)	Larynx toxicity %
VALCSG (7)	332	LC	III–IV	FP	RT	64	68	NR
EORTC24891 (6)	202	HPC	II–IV	FP	RT	22@5 years	38@5 years	NR
RTOG91-11 (62)	547	LC	III–IV	FP	RT/CRT	71/84@5 years	59/55@5 years	6–10/6–17
GORTEC2000-01 (60)	213	LC and HPC	III–IV	FP/TPF	RT	57/70@3 years	60/60@3 years	13.6/6.2
GETTEC (63)	68	LC	II–IV	FP	RT	42	69@2 years	NR
Posner (22)	166	LC and HPC	III–IV	FP/TPF	CRT	32/52@3 years	40/57@3 years	NR
TREMPLIN (55)	153	LC and HPC	III–IV	TPF	CRT/BRT	93/96@3 months	85/86@1.5 years	8.6/9
Prades (61)	71	HPC	III–IV	FP	RT/CRT	68/92@2 years	36/41@2 years	NR

VALCSG, Veterans Affairs Laryngeal Cancer Study Group; LC, laryngeal cancer; HPC, hypopharyngeal cancer; IC, induction chemotherapy; FP, 5FU and ccisplatin, TPF, docetaxel, 5FU and cisplatin, RT, radiotherapy; CRT, chemoradiotherapy; BRT, bioradiotherapy; LP, laryngeal preservation; NR, note reported.

Table 3. Reported series of randomized control trial comparing IMRT to conventional radiotherapy for head and neck carcinoma

Author	Site	Number	Control	Stage I/II (%)	Chemoradiotherapy	6 months–1 year xerostomia IMRT	6 months–1 year xerostomia conv.	LC (%)	OS (%)
Pow (12)	NPC	45	2D	100	No				
Kam (14)	NPC	54	2D	100	No	39.3	82.1		
Nutting (13)	H&N	94	2D	24	Yes	15	74	NS	NS
Gupta (11)	H&N	60	3D	20	Yes	28.8	76	NS	NS
Peng (15)	NPC	616	2D	31	Yes	28.1	57.4	F	F

NPC, nasopharyngeal carcinoma; H&N, head and neck carcinoma; 2D, two dimensional; 3D, three dimensional; IMRT, intensity modulated radiotherapy; conv., conventional radiotherapy; LC, local control; NS, not significantly different; F, IMRT group is favorable.

cancer (NPC) patients, and the findings obtained revealed that xerostomia was subjectively and/or objectively lower in the IMRT arm than in the 2D RT arm (12,14). Nutting et al. (13) reported the findings of a multi-institutional RCT that compared IMRT with 2D RT for OPC and HPC patients. The xerostomia rates at 1 and 2 years were significantly lower in the IMRT group (38 and 29%) than in the 2D RT group (74 and 83%). OS and loco-regional relapse-free survival LRPFS in both groups were not significantly different between both arms. These findings were also supported by a systematic review (16) (Level Ia). Marta et al. (16) conducted a meta-analysis on five trials comprising 871 patients, including 82% of NPC patients and 62% of patients with Stage III/IV disease. The rate of Grade 2–4 xerostomia was lower in the IMRT group [HR = 0.76, 95% confidence interval (CI) 0.66–0.87; $P < 0.00001$); however, no significant differences were observed in OS or LC between both groups. Over 80% of cohorts received concomitant chemotherapy during IMRT. CCRT is believed to increase the rates of both acute and late toxicities; thus, these findings could be extrapolated on to cases of chemo-IMRT.

IMRT is considered to improve QOL, and a previous systemic review chiefly assessed patient statuses (17,18,19,20) using questionnaires for EORTC C-30, EORTC QLQ H&N35 and SF-35 (Table 4). Tribius et al. (20) performed a systemic review using literature describing QOL assessments between 2005 and 2010. This review assessed 14 studies including five prospective trials with only one RCT. IMRT significantly improved QOL scores comprising xerostomia, dry mouth, sticky saliva, eating-related domains and global QOL over those achieved with 2D or 3D CRT. Klein et al. (19) also performed a systematic review on health-related QOL (HRQOL) scores between IMRT and 2D or 3D CRT. Eighteen studies having high-quality reports of the basis of quality assessment instrument were reviewed in this report. The HRQOL scores declined after RT and returned to baseline levels within 12 months in all groups. The HRQOL score achieved by IMRT was significantly higher than that of 2D or 3D CRT. The HRQOL score achieved by CCRT was slightly worse. These two reviews were considered to have the distinct weakness of strong biases due to the basis of a retrospective analysis. In addition, QOL was difficult to measure in patients with HNSCC, and global QOL is reflected by various factors relating to patient backgrounds and QOL instruments. The benefit of IMRT for dysphagia was also systematically reviewed from 16 studies (17); however, apparent evidence could not be derived in this review. This was attributed to the reported series being limited by both insufficient assessment methods and outcome descriptions of swallowing function. It was also caused by the lack of reliable measuring instruments for swallowing function including basement assessments, and the reported series also chiefly depended on retrospective analysis. A sophisticated RCT with a multi-institutional design is needed to accurately evaluate the advantages of IMRT regard for global QOL and late toxicities apart from xerostomia.

Optimal method for IMRT

IMRT for LA-HNSCC is routinely performed in a simultaneously integrated boost (SIB) method, in which variable doses are delivered to several CTVs for adjusted risk levels (66). Single-step optimization is typically performed during the radiation schedule, and reducing the time and labor required for treatment preparation appears to be feasible in clinical practice. A radiation dose with a lower risk level, 54–60 Gy over 6.5–7 weeks is often delivered in the SIB technique. Regarding 2D–3D CRT, 40–50 Gy is commonly delivered for prophylactic CTV; however, a slightly larger dose may be needed in the case

Table 4. Comparison of QOL score in IMRT group compared with that of conventional radiotherapy group in reported series

Author	Study design	Patient number	Site	EORTC QLQ-C30					EORTC QLQ-C30 HN&35					
				Global QOL	Physical function	Role function	Cognitive function	Social function	Pain	Swallowing	Speech	Social eating	Dry mouth	Sticky saliva
Pow (12)	Prospective	51	NPC			Y							Y	Y
Fang (80)	Prospective	203	NPC	Y									Y	
Vergeer (81)	Prospective	241	H&N	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y
Fang (82)	Retrospective	356	NPC	Y	Y			Y	Y	Y	Y	Y	Y	Y
Graff (83)	Retrospective	134	H&N						Y	Y		Y	Y	
Huang (84)	Retrospective	307	H&N										Y	

NPC, nasopharyngeal cancer; QOL, quality of life; Y, significantly better for IMRT group.

of SIB due to the small fraction size (<1.8 Gy per fraction), which is expected to decrease the probability of disease control. An increased dose to the surrounding organ, such as the larynx and constrictor muscle, may lead to the development of dysphagia (8,67,68). Another weakness of the SIB technique is dose variations due to anatomical changes during the IMRT session. Several studies reported that anatomical changes may cause significant shortages in the dose on PTV and/or an excessive dose to the surrounding organ (69,70). A two-step method would resolve these problems by using the standard fraction size to all target volumes with a second boost IMRT plan (69,71,72). Although the burden on staff would increase due to additional optimization processes, dose variations resulting from anatomical changes due to tumor shrinkage and body weight loss could be adjusted for. The JCOG 1015 (UMIN000005448) is a Phase II trial that is being conducted to demonstrate the feasibility of two-step IMRT with CCRT for Stage II–IVB NPC patients. A total of 75 patients are planned to have registered by October 2014, and a follow-up will be conducted until 2017. The JCOG 1208 (UMIN000014274) is a Phase II trial conducted on patients with OPC of T1–2N0–1 category, and a two-step method is also used in this trial. These multi-institutional prospective trials are expected to demonstrate the original efficacy of the two-step IMRT method for HNSCC patients.

Japanese clinical trials for HNSCC

The JCOG Radiation Therapy Study Group developed a multi-institutional Phase II trial (JCOG 0403) on stereotactic body radiotherapy for Stage I non-small cell lung cancer in 2003. The group then expanded the trial to include several prospective trials including those for HNSCC. To date, the group has conducted a multi-institutional RCT trial to demonstrate the efficacy of AF for glottic cancer of the T1–2N0 category (JCOG 0701), a Phase II trial on chemo-IMRT for LA-NPC (JCOG 1015), and a Phase II trial on IMRT for early OPC (JCOG 1208). The Head and Neck Cancer Study Group of JCOG has conducted a Phase II/III study on post-operative chemoradiotherapy for LA-HNSCC, comparing the administration of cisplatin in a three weekly arm to a weekly arm (JCOG 1008) (73). This trial has made amendments for the use of IMRT in credentialed institutes in collaboration with the Radiation Therapy Study Group.

Apart from the JCOG group trial, a Phase II trial is being conducted on chemo-IMRT for cervical esophageal cancer (JROSG 12-1 UMIN000009880) and is supported by a National Grant Aid. The findings of these prospective trials will greatly impact on Japanese clinical practices and future trials.

Future perspective

Proton beam therapy (PBT) is expected to have the advantage of sparing normal tissue over photon beam. As for carbon-ion therapy, the high value of its relative biological effect may be beneficial for tumor control. A systemic review has discussed the benefits of particle therapy (74,75). Regarding carbon-ion therapy, survival advantages for mucosal malignant melanomas would be reported to some extent (75). The advantages of PBT for survival and tumor control in paranasal and sinonasal cancers have been reported previously (76). However, limited clinical data are available to demonstrate that toxicity is slightly lower for PBT than for photon therapy. Since the overall quantity and quality of data regarding particle therapy is poor, prospective multi-institutional data are needed in the future (75). Intensity modulated proton therapy (IMPT) is one of the promising methods that can improve the quality of definitive RT for HNSCC (75,77). IMPT has the distinct advantage of sparing normal tissue, especially with low dose exposure (77). IMPT is expected to have further advantages; thus, prospective trials on IMPT are warranted to demonstrate its benefits over IMRT.

Biomarkers play important roles in the selection of treatment modalities and/or estimation of treatment outcomes; however, reliable information has not yet been reported for HNSCC. Biomarkers to predict the outcome of CCRT and BRT are needed (78,79), and would be very helpful for both decision-making for optimal treatments and reduction of intensive multidisciplinary therapy.

Conclusion

AF, CCRT and BRT have advantages over standard fractionated radiotherapy; however, the management of both acute and late toxicities has become more important in clinical practice. Although CCRT using high dose cisplatin is the mainstay for LA-HNSCC, late toxicities were reported to increase in association with survival disadvantages. IMRT is believed to be useful for minimizing morbidity and mortality related to definitive RT, especially in the case of CCRT. Further improvements are warranted through the optimal use of adaptive radiotherapy and particle therapy.

Multi-agent induction chemotherapy with BRT represents on attractive option for balancing efficacy and toxicity, and is now being eagerly tested in prospective trials. In the future, customized therapy designed with biomarkers is desired to optimize definitive radiotherapy.

Acknowledgements

We wish to express our special appreciation to all the staff at the participating institutes of JCOG 0701, JCOG 1008, JCOG 1015 and JCOG 1208 trial, and JCOG Data Center.

Funding

The work was partially supported by Health Sciences Research Grants for a Grant-in-Aid for Cancer Research (20S-5, 20S-6, 17-17, 16-12, 17S-5 H21-018, H23-009, H24-007, H26-090) from the Ministry of Health, Labor and Welfare of Japan and the National Cancer Center Research and Development Funds (23-A-16, 23-A-21 and 26-A-4).

Conflict of interest statement

None declared.

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