Published in final edited form as:

Leuk Lymphoma. 2020 October ; 61(10): 2442–2447. doi:10.1080/10428194.2020.1768388.

Potential Impact of Consolidation Radiation Therapy for Advanced Hodgkin Lymphoma: a Secondary Analysis of SWOG S0816

Chul S. Ha, MD¹, Michael LeBlanc, PhD², Heiko Schöder, MD³, Chelsea C. Pinnix, MD,Ph.D⁴, Nancy L. Bartlett, MD⁵, Andrew M. Evens, DO, MSc⁶, Eric D. Hsi, MD⁷, Lisa Rimsza, MD⁸, Michael V. Knopp, MD, PhD⁹, Jun Zhan, PhD⁹, John P. Leonard, MD¹⁰, Brad S. Kahl, MD⁵, Hongli Li, MS², Sonali Smith, MD¹¹, Louis S. Constine, MD^{12,*}, Jonathan W. Friedberg, MD^{12,*}

¹University of Texas Health Science Center at San Antonio, TX

²SWOG Statistical Center; Fred Hutchinson Cancer Research Center, Seattle, WA

³Memorial Sloan Kettering Cancer Center, New York, NY

⁴MD Anderson Cancer Center, Houston, TX

⁵Washington University School of Medicine, St. Louis, MO

⁶Rutgers Cancer Institute, New Brunswick, NJ

⁷Cleveland Clinic, Cleveland, OH

⁸Mayo Clinic, Scottsdale, AZ

⁹The Ohio State University, Columbus, OH

¹⁰Weill Cornell Medical Center, New York, NY

¹¹University of Chicago, Chicago, IL

¹²Wilmot Cancer Institute, University of Rochester, Rochester, NY

Abstract

The role of radiotherapy (RT) in the management of advanced Hodgkin Lymphoma (HL) is inadequately defined in this era of functional imaging with PET scan. SWOG-S0816 treated advanced stage Hodgkin lymphoma patients with ABVD+/- escBEACOPP and no RT. We queried whether RT might have benefited patients in S0816 who would have met the GHSG-HD15 criteria for RT by simulating RT use as per HD15 criteria of PET+ residual disease ≥ 2.5 cm. Receiver-operating-characteristics analyses were performed by varying disease-control rates within radiation fields and size cut-offs for residual disease. Among the 49 PET3+ S0816 patients, RT would have raised the 2-year PFS from 30.6% to 50.2–58.1% using three residual disease cut-offs

Corresponding Author: Chul S. Ha, M.D., Department of Radiation Oncology, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, Hac@uthscsa.edu, Phone (210) 450-5566.

*Equal Contribution

Clinical Trial Information: Secondary analysis for SWOG S0816

(1.5, 2.0 and 2.5 cm) and assuming 80 and 90% in-field control rates. Although there may be improvement in PFS as size cut-off point is lowered, consequential toxicities from RT require further definition to assess relative benefits.

Keywords

Hodgkin lymphoma; radiotherapy; PET (positron emission tomography)

Introduction

The role of RT in the management of advanced HL is inadequately defined in this era of functional imaging with PET.[1] Two randomized trials prior to the PET era, one by the European Organization for Research and Treatment of Cancer Lymphoma Group (EORTC 20884) involving hybrid chemotherapy with mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (MOPP-ABV) and the other by the German Hodgkin Study Group (GHSB HD12) involving chemotherapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP), demonstrated no benefit of consolidation RT for patients achieving a complete response to chemotherapy but potential benefit to those achieving a partial response or with residual disease upon subgroup analyses.[2,3] A meta-analysis of 14 randomized trials of chemotherapy versus combined modality, with the caveat that radiation fields were mostly involved or extended fields compared to the currently used involved site fields, reported a significantly inferior long-term survival with combined modality compared to chemotherapy alone given over appropriate number of cycles.[4] The GHSB HD15 was a randomized trial comparing 3 different BEACOPP regimens for newly diagnosed advanced Hodgkin lymphoma. Patients with stage IIB disease with large mediastinal mass or extranodal lesions and all patients with stages III and IV were eligible. Consolidation RT to a dose of 30 Gy at 1.8–2.0 Gy per fraction was delivered to the FDG-PET positive residual disease measuring at least 2.5 cm,[5] achieving an in-field control rate of 91.5% with median follow-up of 102 months (personal communication with A. Engert). PET positivity was determined by a central review panel. Compared to the previous GHSB HD9 trial,[6] the addition of PET-CT to response assessment resulted in a smaller proportion of patients receiving RT (70% vs 11%). Patients with persistent PET positivity in a residual mass measuring at least 2.5 cm after completion of chemotherapy (n=191) had excellent protocol adherence with 92% receiving RT and achieving excellent 4-year PFS of 86.2%.

SWOG S0816 was a US intergroup trial utilizing ABVD-based therapy with response adaptation based on interim FDG-PET imaging. RT was not allowed per protocol, and counted as an event.[7,8] In the initial report of the study 32% of progressions occurred in sites of previous disease, and but only 2 relapses were in initial sites of >10 cm bulk involvement.[7] In this secondary analysis of SWOG S0816, we have addressed the question “What impact would consolidation RT per GHSB HD15 guidelines have in PFS for patients treated on S0816?”

Materials and Methods

Patients with measurable stage III to IV classic Hodgkin lymphoma, without prior therapy for lymphoma, age 18 to 60 years and Zubrod performance status 0 to 2, were eligible for SWOG S0816.[7] Patients who achieved negative PET scan (5PS, 1 to 3) after 2 cycles of ABVD chemotherapy (PET/CT #2) proceeded with 4 more cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), followed by an end of treatment PET-CT scan (PET/CT #3) which was obtained 6–8 weeks after the end of therapy. Patients with a positive interim PET/CT #2 scan (5PS, 4 to 5) were switched to 6 cycles of escalated BEACOPP, followed by PET/CT #3. We identified patients who have been coded as having positive PET/CT #3. Their PET/CT #3 scans were reviewed again by one of the coauthors (H.S.) who had been one of the central reviewers of the scans for the initial publication of the study,[7] using NM viewer application (IntelliSpace Portal 6.0 workstation by Philips Healthcare). Volumetric regions of interest were placed around sites of FDG-avid residual disease. Volumetric regions of approximately 1 cm³ were placed in the ascending aorta (Mediastinal Blood Pool) and the posterior right lobe of the liver for measurements of reference background activity.

Statistical Methods

We simulated the PFS assuming radiation had been delivered per HD15 criteria (PET/CT #3 positive disease ≥ 2.5 cm) following their radiation guidelines.[9] There was no limit in the number of sites that could be radiated. Receiver operating characteristics (ROC) analyses were performed by varying the local control rates within the radiation fields (80% and 90%) and also by varying the size cut-off points for the residual disease (≥ 1.5 cm, ≥ 2.0 cm and ≥ 2.5 cm). These cut-offs were selected as we wanted to study the impact of lowering the threshold for RT on consequential PFS. The actual simulation model induced local control “cure” fractions as specified above. Simulated curves with different cure rates can be generated by repeatedly randomly assigning cured patients to the fraction of control rates specified. However, the expected simulation result was calculated by including case-level weight functions into the Kaplan-Meier estimators[10] of the local control distribution. All calculations were done in the R statistical language. We also performed a multivariate Cox regression model analysis including tumor mass to investigate the impact of PET/CT #2 status (positive or negative) on PFS and OS.

Results

Of a total of 358 HIV negative patients enrolled in the protocol, 336 of them were eligible and evaluable. Long-term outcomes for the trial have been recently published.[8] Forty-nine patients (15%) were identified to have positive PET/CT #3. Among the 49 patients, 17 had positive PET/CT #2; sixteen of them actually received escalated BEACOPP and one continued on ABVD. The median follow-up for these 49 patients was 71 months (range 9.7–92.6). Their estimated 5-year overall survival was 83% (95% CI: 68%–91%). Their observed landmark PFS at 2 years after the date of PET/CT #3 was 30.6% (95% CI: 18%–44%). Twenty-four (49%), 33(67%), and 40 (82%) of the 49 patients had at least one site of disease that met the HD15 criteria for radiation with ≥ 2.5 cm, ≥ 2.0 cm, and ≥ 1.5 cm size

cut-offs respectively. Sixteen, 19, and 25 patients had disease progression or relapse, respectively, from each group at a median of 1.4–1.5 months. Twelve, 12, and 15 patients had progression/relapses limited to the sites that would have been radiated following HD15 criteria with 2.5 cm, 2.0 cm, and 1.5 cm respectively. These are the patients whose relapse could have been prevented by consolidation RT. Estimated landmark PFS at 2 years for the 49 PET/CT #3 positive patients, assuming 80% and 90% control of the disease within the radiated sites following HD15 guideline with 2.5 cm, 2.0 cm, and 1.5 cm cut-offs, is summarized in columns A and B of the table 1. Figure 1 depicts the landmark PFS for the 49 PET/CT #3 positive patients with 2.5 cm size cut-off assuming 80% and 90% control of the disease within the radiated sites compared to the study (observed PFS). The estimated hazard ratios between the 80% control and observed data and between 90% control and observed data are 0.62 and 0.58 respectively. The approximate 95% confidence intervals, calculated to give a sense of sampling error for new hypothetical studies of the same size and event rate, for these hazard ratios would be 0.37–1.03 and 0.34–0.96 respectively. The landmark PFS does not start at 100% since the time 0 for the landmark PFS is at the time of PET/CT #3 and some patients are declared to have recurrence at the time of PET/CT #3. Of note, 13 patients relapsed in sites that did not have FDG avidity. The multivariate Cox regression model including tumor mass showed no additional effect of PET/CT #2 status ($p=0.14$ for PFS and $p=0.3$ for OS).

Discussion

Adaptive therapy based on FDG-PET imaging has been extensively investigated recently in the management of HL.[11] The results of interim FDG-PET imaging have been studied as a tool to either escalate or de-escalate the intensity of treatments in advanced HL.[7,12–14] The role of consolidation RT after complete metabolic response to 6 cycles of ABVD in patients with advanced disease has been addressed in the GITIL/FIL HD 0607[13] and FIL HD0801 trials,[15] with one study showing no benefit and the other potential benefit for patients with bulky (>5cm) disease. The role of RT for patients with positive FDG-PET imaging after completion of planned chemotherapy in the setting of advanced disease has not been studied in a randomized trial. Typically only a small fraction of patients will have PET positive residual disease after completion of planned chemotherapy. Consequently a large number of patients would need to be enrolled on a clinical trial to assess the efficacy and toxicity of adjuvant RT in a randomized fashion.

This study was devised to model the potential benefit of consolidation RT for such a study population. SWOG S0816 is an ideal trial to examine this issue in advanced stage HL patients since no RT was allowed. We applied the criteria for consolidation RT based on GHSG HD15. These criteria have a long track record of clinical application as they evolved from GHSG HD12 and continued through HD18.[3,16] Of note, consolidation RT per HD15 was based on CT and PET criteria and biopsy of the residual disease was not required. This contrasts with another approach of obtaining biopsy of the PET positive lesions at the end of systemic therapy. If biopsy is positive, salvage systemic therapy followed by stem cell rescue and RT is an acceptable standard of care. If biopsy is negative, a further follow-up with another PET scan may be recommended. The patients in HD15 were treated with 6–8 cycles of BEACOPP-based regimens while the vast majority of our patients were treated with 6

cycles of ABVD. Though the patients with end-of-(systemic) treatment PET/CT positivity from these 2 protocols may have different prognosis due to different induction chemotherapy regimens, the focus of our modeling is on the potential value of consolidation radiation therapy to PET positive lesions at the end-of-(systemic) treatment, regardless of the components of the induction therapy. As the multivariate Cox regression model showed no additional effect of PET2 status on PFS and OS, we decided not to perform a separate analysis for the subgroup of patients with positive PET/CT #2. However, we should note that the absence of additional effect of PET2 status could be a consequence of an escalation of therapy based on PET2 status. We also performed ROC analyses by applying a range of size cut-offs for the residual disease along with a range of control probabilities within the virtual radiation fields. As can be seen from the Table 1 and Figure 1, consolidation RT could have augmented the 2-year landmark PFS by 20–28% for the 49 patients with positive PET/CT #3. The magnitude of improvement in PFS will increase as the size cut-off gets smaller. However, smaller size cut-off means more patients are to be radiated, emphasizing the need for optimal definition of the size cut-off. Currently used 2.5 cm residual tumor size has evolved from 1.5 cm used for HD12 without the use of PET scans to 2.5 cm for HD15 and HD18 with the use of PET scans.

This study was designed to assess the potential impact of consolidation RT for patients with PET positive residual disease upon completion of chemotherapy for HL. Clearly this impact (or potential benefit) must be weighed against the side effects (or potential risks) of RT. Though the acute side effects of RT have been greatly reduced with the introduction of more limited volume involved site RT,[17] long-term risks remain to be defined with these new strategies. We did not exclude the patients who had a relapse immediately after completion of chemotherapy. One reason is the timing of PET/CT #3 was 6–8 weeks (more variation in actuality) after the end of chemotherapy for SWOG S0816 while the end-of-treatment PET for HD15 was at least 2 weeks after completion of chemotherapy. Hypothetically we could have caught PET/CT #3 positive patients earlier if it had been done sooner than 6–8 weeks after completion of chemotherapy. And this might have allowed time for RT to be administered before frank progression of the disease. The other reason is due to the subjectivity associated with declaring a particular day as “date of relapse” since PET/CT #3 positive date is not necessarily the relapse date. Our modeling is intended to show the full range of potential benefits of consolidation RT. It is possible that some patients might have missed the “window of opportunity” for consolidation RT. However, it is impossible to figure out the actual number of patients, given the 6–8 week lag from the end of chemotherapy. Our modeling has been designed to calculate the “best scenarios” in the situation with PET positive residual disease at the end of chemotherapy. In addition, our modeling does not take each patient’s lymphoma biology or the biological effect of RT beyond the local control rate. For example, we could not account for how radiation field(s) would affect the individual patient’s immune system and thereby the pattern of recurrence.

Oncologists must personalize the risk/benefit ratio for each patient depending on multiple factors such as age, gender, performance status of the patient as well as the location(s) of the residual disease. Though we did not have adequate sample size to analyze the significance of biomarkers such as serum thymus and activation-related chemokine and interleukin-10[18]

for our patient population with PET3 positive disease, we expect that biomarkers should assist in the selection of patients who might benefit most from RT in the future.

Although response-adapted therapy using FDG-PET imaging appears to improve outcomes for patients with advanced stage Hodgkin lymphoma who are interim PET positive, the majority of relapses have occurred in patients who are interim PET negative, demonstrating limitations of this approach.[8] Metabolic tumor volume, maximum standardized uptake value reduction between the baseline and interim PET, and total lesion glycolysis have emerged as potentially useful prognostic indicators in the management of lymphoma and deserve further study as a means to help define the optimal use of RT.[19–21] Moving forward, the National Clinical Trials Network has developed SWOG S1826, a randomized trial comparing AVD-brentuximab to AVD-nivolumab in patients with advanced stage Hodgkin lymphoma ages 12 and above ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03907488) Identifier: [NCT03907488](https://clinicaltrials.gov/ct2/show/study/NCT03907488)). This trial will not incorporate PET adaptation, however, allows RT at investigator discretion for patients with residual (≤ 2.5 cm for nodal and > 1 cm for extranodal lesion) PET avid disease with ≥ 30% reduction in maximum transverse diameter upon completion of systemic therapy. RT to more than 2 nodal sites is not allowed, and we are using the end-of-systemic therapy PET result to decide on the consolidation radiation therapy in S1826, based upon the results of this modeling exercise.

In conclusion, consolidation RT for patients with advanced HL confers potential morbidities despite the small irradiated volumes that can include sensitive tissues; however, this does not obviate a relatively substantial benefit for the limited patient population with PET positive residual disease who might be spared relapse and the attendant therapies such as salvage chemotherapy and autologous stem cell transplant. New response measures using PET imaging and further defining patients vulnerable to recurrent disease who benefit from consolidative RT should be important goals of future randomized trials.

Acknowledgments:

This study is presented in memory of Oliver W. Press, M.D., Ph.D., Principal Investigator of S0816, mentor, scientist, colleague and friend.

Funding Statements: This investigation was supported in part by National Institutes of Health/National Cancer Institute/ National Clinical Trials Network grants CA180888, CA180819, CA180821, CA180820, UG1CA233339, CA180833, CA180818, CA11083, and CA04919. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure of Conflicts of Interest:

DMS has received research funding from Acerta, Gilead, Karyopharm and honoraria from Genentech. HS has served as a consultant for Allero Therapeutics. DJS has received research funding and serves as a consultant for Seattle Genetics. LMR holds a patent through NanoString. NLB has received research funding from Gilead, Kite, Seattle Genetics, Affimed, Bristol-Meyers Squibb, Celgene, Forty Seven, Genentech, Immune Design, Janssen, Merck, Millennium, and Pharmacyclics. She serves as a consultant for Pfizer and Acerta. AME serves as a consultant and has received honoraria from Seattle Genetics, Bayer, Verastem, and Pharmacyclics. ASL serves as a consultant for Seattle Genetics and Bristol Myers Squibb. PRB serves as a consultant for Abbvie. EDH serves as a consultant for Celgene, Seattle Genetics, and Jazz and has received research funding from Abbvie and Eli Lilly. JPL serves as a consultant for Celgene, Juno, Bristol Meyers Squibb, Sutro, Gilead, Genentech, Pfizer, Bayer, Biotest, United Therapeutics, Karyopharm, ADC Therapeutics, MEI Pharma, AstraZeneca, and Novartis. BSK serves as a consultant for Genentech, Celgene, Acerta, AstraZeneca, Juno, CTI, ADC Therapeutics, Abbvie, Gilead, and Seattle Genetics. SMS serves as a consultant for Bristol Meyers Squibb, Humanigen, and Seattle Genetics and has received research funding from Forty Seven and Sanofi. JWF has received honoraria from Bayer.

References

1. Specht L. Does Radiation Have a Role in Advanced Stage Hodgkin's or Non-Hodgkin Lymphoma? *Curr Treat Options Oncol*. 2016 1;17(1):4. [PubMed: 26739151]
2. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med*. 2003 6 12;348(24):2396–406. [PubMed: 12802025]
3. Borchmann P, Haverkamp H, Diehl V, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. *J Clin Oncol*. 2011 11 10;29(32):4234–42. [PubMed: 21990399]
4. Loeffler M, Brosteanu O, Hasenclever D, et al. Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease Overview Study Group. *J Clin Oncol*. 1998 3;16(3):818–29. [PubMed: 9508162]
5. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012 5 12;379(9828):1791–9. [PubMed: 22480758]
6. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol*. 2009 9 20;27(27):4548–54. [PubMed: 19704068]
7. Press OW, Li H, Schoder H, et al. US Intergroup Trial of Response-Adapted Therapy for Stage III to IV Hodgkin Lymphoma Using Early Interim Fluorodeoxyglucose-Positron Emission Tomography Imaging: Southwest Oncology Group S0816. *J Clin Oncol*. 2016 6 10;34(17):2020–7. [PubMed: 27069074]
8. Stephens DM, Li H, Schoder H, et al. Five-Year Follow-up of SWOG S0816: Limitations and Values of a PET-Adapted Approach for Stage III/IV Hodgkin Lymphoma. *Blood*. 2019 7 22.
9. Kriz J, Reinartz G, Dietlein M, et al. Relapse analysis of irradiated patients within the HD15 trial of the German Hodgkin Study Group. *Int J Radiat Oncol Biol Phys*. 2015 5 1;92(1):46–53. [PubMed: 25863753]
10. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed*. 2004 7;75(1):45–9. [PubMed: 15158046]
11. Diefenbach CS, Connors JM, Friedberg JW, et al. Hodgkin Lymphoma: Current Status and Clinical Trial Recommendations. *J Natl Cancer Inst*. 2017 4;109(4).
12. Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol*. 2019 1 15.
13. Gallamini A, Tarella C, Viviani S, et al. Early Chemotherapy Intensification With Escalated BEACOPP in Patients With Advanced-Stage Hodgkin Lymphoma With a Positive Interim Positron Emission Tomography/Computed Tomography Scan After Two ABVD Cycles: Long-Term Results of the GITIL/FIL HD 0607 Trial. *J Clin Oncol*. 2018 2 10;36(5):454–462. [PubMed: 29360414]
14. Johnson P, Federico M, Kirkwood A, et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. *N Engl J Med*. 2016 6 23;374(25):2419–29. [PubMed: 27332902]
15. Ricardi U, Levis M, Evangelista A, et al. Role of consolidation RT to bulky lesions of advanced Hodgkin lymphoma: Results of FIL HD0801 trial. *Radiotherapy and Oncology*. 2019;133:s258.
16. Borchmann P, Haverkamp H, Lohri A, et al. Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with BEACOPPescalated alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. *Lancet Oncol*. 2017 4;18(4):454–463. [PubMed: 28236583]
17. Specht L, Yahalom J, Illidge T, et al. Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014 7 15;89(4):854–862. [PubMed: 23790512]

18. Hsi ED, Li H, Nixon AB, et al. Serum levels of TARC, MDC, IL-10, and soluble CD163 in Hodgkin lymphoma: a SWOG S0816 correlative study. *Blood*. 2019 4 18;133(16):1762–1765. [PubMed: 30723079]
19. Schoder H, Moskowitz C. Metabolic Tumor Volume in Lymphoma: Hype or Hope? *J Clin Oncol*. 2016 9 06.
20. Rossi C, Kanoun S, Berriolo-Riedinger A, et al. Interim 18F-FDG PET SUVmax reduction is superior to visual analysis in predicting outcome early in Hodgkin lymphoma patients. *J Nucl Med*. 2014 4;55(4):569–73. [PubMed: 24566003]
21. Guo B, Tan X, Ke Q, et al. Prognostic value of baseline metabolic tumor volume and total lesion glycolysis in patients with lymphoma: A meta-analysis. *PLoS One*. 2019;14(1):e0210224. [PubMed: 30625203]

Figure 1.

Landmark progression free survival for 49 PET3 positive patient with varying rates of local control within the radiation fields following HD15 radiation criteria of 2.5 cm

Table 1:

Estimated 2-year landmark PFS for 49 PET/CT #3 positive patients with ROC analysis. (The observed point estimate for 2-year PFS is 30.6%.)

	A (80% local control)	B (90% local control)
PET3+ 2.5 <i>cm</i>	50.2 %	52.7 %
PET3+ 2.0 <i>cm</i>	50.2 %	52.7 %
PET3+ 1.5 <i>cm</i>	55.1 %	58.1 %