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EDITORIAL

New endoscopy advances to refine adenoma detection rate for colorectal cancer screening: None is the winner

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Abstract

Colorectal cancer (CRC) is the third most common cancer in males and second in females, and globally the fourth cause for cancer death worldwide. Oncological screening of CRC has a major role in the management of the disease and it is mostly performed by colonoscopy. Anyway, effectiveness of endoscopic screening for CRC strictly depends on adequate detection and removal of potentially precancerous lesions, and accuracy of colonoscopy in detection of adenomas is still suboptimal. For this reason, several technological advances have been implemented in order to improve the diagnostic sensitivity of colonoscopy in adenoma detection. Among these: (1) Visual technologies such as chromoendoscopy and narrow band imaging; (2) optical innovation as high definition endoscopy, full-spectrum endoscopy or Third Eye Retroscope; and (3) mechanical advances as Cap assisted colonoscopy, Endocuff, Endoring and G-Eye endoscope. All these technologies advances have been tested over time by clinical studies with mixed results. Which of them is more likely to be successful in the next future?

Key words: Colorectal cancer screening; Colonoscopy; Adenoma detection rate; Diagnostic advances

Core tip: Oncological screening of colorectal cancer is mostly performed by colonscopy and effectiveness of this technique strictly depends on adequate detection and removal of potentially precancerous lesions. Anyway, accuracy of colonoscopy in detection of adenomas is still suboptimal. For this reasons several technological advances have been implemented in order to improve the diagnostic sensitivity of colonoscopy in adenoma detection. Which of them is more likely to be successful in the next future?

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in males and second in females, and globally the fourth cause for cancer death worldwide[1,2]. Oncological screening of CRC has a major role in the management of the disease, since several randomized controlled trials demonstrated an increase in 5-year survival and a reduction in mortality for healthy subject undergoing surveillance, compared to patients who are diagnosed in the clinical phase of the disease[3]. To date several tests have been used in CRC screening, among them fecal occult blood test, fecal DNA test, sigmoidoscopy, colonoscopy and computed tomographic colonography. Anyway colonoscopy has a pivotal role in CRC screening, since it can be used both as primary screening test, both as recall strategy after a positive result of a different test in order to confirm diagnosis and provide removal of polyps. Since effective endoscopic screening for CRC strictly depends on adequate detection and removal of potentially precancerous lesions, over time performance measures and quality indicators have been assessed in order to ensure the quality of the examination and improve patient outcomes[4-6].

The European Society of Gastrointestinal Endoscopy and United European Gastroenterology have recently presented a short list of key performance measures for lower gastrointestinal endoscopy[7]. Among these, cecal intubation rates, withdrawal times, quality of bowel preparation and adenoma detection rate (ADR).

ADR is the primary quality indicator for colonoscopy and depends by the performance of the endoscopist. It is defined as the proportion of screening colonoscopies in patients aged 50 years or older detecting at least one adenoma, and it should be ideally at least 25%. A first study in 2010 showed that ADR is an independent predictor of the risk of interval CRC after screening colonoscopy[8] and a recent prospective study of individuals who underwent screening colonoscopy within a National Colorectal Cancer Screening Program, showed that increased ADR is associated with reduced risk of interval CRC and death[9]. Anyway, despite quality measures, the accuracy of colonoscopy in detection of adenomas is still suboptimal[10]. Up to date several technological advances have been implemented in order to improve the diagnostic sensitivity of colonoscopy in adenoma detection.

First of all visual and optical enhancement technologies have been introduced with the aim of improve ADR. In the group of visual enhancement advances, chromoendoscopy and narrow band imaging (NBI) have been test over time. As suggested by a Cochrane review, chromoendoscopy can improve detection of polyps, anyway it is a time-consuming technique and it is not always feasible in real practice[11]. Contrariwise, as showed by several studies, NBI does not improve ADR during colonoscopy[12,13]. Among optical innovation, high definition endoscopy (HDE), using high definition monitor and a high resolution charge coupled device with up to a million pixels, allows a better image view compared to standard vision endoscopy (SVE). Anyway studies report conflicting results. A recent meta-analysis comparing high definition *vs* standard video endoscopy showed, in favor of HDE, an incremental yield of 3.8% (95%CI: 1%-6.7%) for the detection of any polyp, an incremental yield of 3.5% (95%CI: 0.9%-6.1%) for detection of adenomatous polyps and no differences between HDE and SVE in the detection of high-risk adenomas[14].

The full-spectrum endoscopy (FUSE, EndoChoice, GA, United States) is a new technology using a colonoscope equipped with two lateral lenses, in addition to the one on the forward tip, so to increase the maximum field of view up to 330°, compared to the $\leqslant$ 170° of standard forward-viewing (SFV) colonoscopy. This allows greater visual field and, at least in theory, greater detection rate of polyps.

A multicenter, randomized back-to-back study showed a significantly higher detection rate of adenomas (69% additional adenomas) and a lower adenoma miss rate with FUSE (7%) respect to SFV colonoscopy (41%) ($P < 0.0001$)[15].

Despite this good premise, a randomized controlled trial performed on a large population of patients undergoing colonoscopy following a positive fecal immunochemical test, showed no statistically significant difference in detection rates of adenomas (ADR) and advanced adenomas (defined as adenomas $\geqslant$ 10 mm and/or with villous component > 20%, and/or high-grade dysplasia) in a per patient analysis[16].

Another recent randomized back to back study compared adenoma miss rates of full-spectrum endoscopy (FSC) with those of conventional colonoscopy complemented by right-colon re-examination using scope retroflexion (CC/R) performed by endoscopists with documented ADRs > 35%. FSC showed, by a per-lesion analysis, a significantly lower adenoma miss rate compared with CC/R [10.9% (95%CI: 3.8-18.1) *vs* 33.7% (95%CI: 23.4-44.1)] and a lower advanced adenoma miss rate lower with FSC [4.3% (95%CI: -4.0-12.7) *vs* 25.9% (95%CI: 9.4-42.5)] showing as FSC outperforms conventional colonoscopy even when performed by experienced endoscopists[17]. Therefore, despite its good technical result, so far literature data are conflicting and a definite benefit on ADR has not been yet demonstrated.

One more technological solution is the Third Eye Retroscope (TER; Avantis Medical Systems, Inc), a device that can be inserted through a standard colonoscope's working channel, advanced over the tip and bend to 180 degrees before the withdrawal phase, in order to obtain an additional backward view that increases the visibility of blind areas not fully visible on standard view examination.

Studies performed so far showed a gain in ADR from 13.2% to 23.2%[18,19]. Despite a quite gain in adenoma detection, however the procedure is time consuming and presents some disadvantages such as an inferior image quality, a reduced suction capacity of the scope and the necessity of removing the third eye retroscope whenever another device need to be inserted through the working channel.

One additional method to enhance ADR is that to obtain a mechanical improvement of endoscopic view by a mechanical flattening of haustral folds and tip stabilization. In this line, several devices have been introduced to refine efficiency of the standard colonoscope, such as cap, cuff and rings.

Cap assisted colonoscopy (CAC) is a simple technique utilizing a transparent cap mounted on the tip of a standard colonoscope, with the aim to obtain folds flattening during withdrawal and preventing the collapse of the mucosa against lenses. This device have been originally used during endoscopic submucosal dissection (ESD) and subsequently tested also for diagnostic colonscopy in order to enhance visibility of blind areas and improve ADR. A recent meta-analysis performed on 4 studies compared CAC *vs* standard colonoscopy (SC), showed a higher right ADR (23% *vs* 17%; OR = 1.49, 95%CI: 1.08-2.05; I^2 = 79%; P = 0.01), similar to that obtained with TER, and an improved detection rate of flat adenoma (OR = 2.08; 95%CI: 1.35-3.20; P < 0.01) for CAC respect to SC[20]. Another meta-analysis of 23 RCTs comparing CAC *vs* SC showed an increase in detection rate of polyps (OR = 1.17, P < 0.01), but no statistically significant difference in ADR[21].

One different mechanical solution is Endorings (EndoAid Ltd., Caesarea, Israel), a silicone-rubber device fitted onto the distal end of the colonoscope and composed by flexible circular rings that allow mechanical stretch of colonic folds during withdrawal and stabilize the tip to the center of the lumen. A recent multicenter, randomized study showed that EndoRings colonoscopy compared with standard colonoscopy allows a lower polyp miss rate (9.1% *vs* 52.8%; P < 0.001) and a significantly lower adenoma miss rate (10.4% *vs* 48.3%; P < 0.001)[22].

Similarly to Endorings, Endocuff (Arc Medical, Leeds, United Kingdom) is a plastic mechanical device provided with rows of finger-like projections, which is mounted onto the distal tip of endoscope. During gently insertion of colonoscope, finger projections collapse back, while during withdrawal they flare out allowing a mechanical grip with flattening of the colonic folds and centering the tip in the lumen. Two RCTs showed that colonscopy with Endocuff increase by 63% detection of polyps and by 83% detection of adenoma[23], as well as increase significantly ADR (35% *vs* 21%; P < 0.0001) respect to standard colonoscopy[24].

Contrariwise to these results a subsequent RCT performed on a large number of patients, even showing an higher detection of adenomas sized < 6 mm (443 *vs* 378; P = 0.03) and of flat polyps (213 *vs* 161; P = 0.03), did not found difference in ADR overall between Endocuff and standard colonoscopy[25]. Finally, the use of EndoRings and Endocuff is safe since no major adverse events have been registered so far, while minor drawbacks are the possibility of device detachment from the colonoscope and risk of slight mucosal lacerations.

One of the latest mechanical advances is G-EYE (Smart Medical Systems Ltd). The G-EYE endoscope employs a permanently-integrated balloon at the tip of the standard endoscope, which is moderately inflated at a selected partial pressure during withdrawal, with the aim to straighten colonic folds, centering the tip and enhancing endoscopic visibility. This technique has been assessed in a randomized tandem study showing that G-EYE colonscopy increased ADR by 81% (P < 0.001) and lowered adenoma miss rate (7.5% *vs* 44.7%; P = 0.0002) compared with standard colonoscopy, without significant adverse events[26].

DISCUSSION

Oncological screening have a key role in the prevention of CRC and strong evidences from literature clearly demonstrated an increase in 5-year survival and a reduction in mortality for healthy subject undergoing surveillance. Although colonoscopy is the gold standard for CRC screening, its accuracy is still suboptimal and a significant number of adenomas are still missed during examination, mostly due to inherent limitations of the technique that does not allow a full visualization of hidden points especially the ones behind colonic folds and flexures.

Today one of the most important challenges is that to increase the quality of the endoscopic technique, with the aim to enhance ADR and consequently the effectiveness of oncological screening. On this line, many innovations have been developed with promising results. Between these, HDE showed excellent results in terms of image definition and will probably replace over time the standard definition technology. Similarly, the FUSE showed a spectacular 330° field of view, but recent evidences proved no difference in ADR and it is unlikely that this technology will be further developed in the future. The use third eye retroscope showed a gain in ADR, but this device is burdened by an inferior quality of image and the procedure is often time consuming and not always comfortable.

Mechanical advances such as CAP assisted colonscopy, EndoRings and Endocuff showed promising result in terms of ADR. In addition these solutions are simple to use, economical and safe. Anyway, before recommending a widespread use, further randomized controlled trials are needed in order to better assess performance of these devices. Finally, G-EYE endoscope has been recently introduced and needs further studies.

In conclusion, great technological advances have been made so far, but none of these innovations have been proven to be so effective to be strongly recommended right now in clinical practice worldwide.

Currently existing devices require further assessment, and at the same time new technologies need to be developed.

Waiting for that, we recommend the use of high definition image systems ensuring, at the same time, adherence to quality measures for lower endoscopy, including high cecal intubation rates, withdrawal times of 6 min or longer and optimal quality of bowel preparation.

REFERENCES

1 **Global Burden of Disease Cancer Collaboration**. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park EK, Catalá-López F, deVeber G, Gotay C, Khan G, Hosgood HD 3rd, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrime MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad SM, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Orjuela C, van Gool CH, Violante F, Oh IH, Deribe K, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillmann T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M. The Global Burden of Cancer 2013. *JAMA Oncol* 2015; **1**: 505-527 [PMID: 26181261 DOI: 10.1001/jamaoncol.2015.0735]

2 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

3 **Mandel JS**, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365-1371 [PMID: 8474513 DOI: 10.1056/NEJM199305133281901]

4 **Valori R**, Rey JF, Atkin WS, Bretthauer M, Senore C, Hoff G, Kuipers EJ, Altenhofen L, Lambert R, Minoli G; International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Quality assurance in endoscopy in colorectal cancer screening and diagnosis. *Endoscopy* 2012; **44** Suppl 3: SE88-SE105 [PMID: 23012124 DOI: 10.1055/s-0032-1309795]

5 **Rembacken B**, Hassan C, Riemann JF, Chilton A, Rutter M, Dumonceau JM, Omar M, Ponchon T. Quality in screening colonoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE). *Endoscopy* 2012; **44**: 957-968 [PMID: 22987217 DOI: 10.1055/s-0032-1325686]

6 **Rex DK**, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM; ASGE/ACG Taskforce on Quality in Endoscopy. Quality indicators for colonoscopy. *Am J Gastroenterol* 2006; **101**: 873-885 [PMID: 16635231 DOI: 10.1111/j.1572-0241.2006.00673.x]

7 **Kaminski MF**, Thomas-Gibson S, Bugajski M, Bretthauer M, Rees CJ, Dekker E, Hoff G, Jover R, Suchanek S, Ferlitsch M, Anderson J, Roesch T, Hultcranz R, Racz I, Kuipers EJ, Garborg K, East JE, Rupinski M, Seip B, Bennett C, Senore C, Minozzi S, Bisschops R, Domagk D, Valori R, Spada C, Hassan C, Dinis-Ribeiro M, Rutter MD. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. *Endoscopy* 2017; **49**: 378-397 [PMID: 28268235 DOI: 10.1055/s-0043-103411]

8 **Kaminski MF**, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, Zwierko M, Rupinski M, Nowacki MP, Butruk E. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med* 2010; **362**: 1795-1803 [PMID: 20463339 DOI: 10.1056/NEJMoa0907667]

9 **Kaminski MF**, Wieszczy P, Rupinski M, Wojciechowska U, Didkowska J, Kraszewska E, Kobiela J, Franczyk R, Rupinska M, Kocot B, Chaber-Ciopinska A, Pachlewski J, Polkowski M, Regula J. Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. *Gastroenterology* 2017; **153**: 98-105 [PMID: 28428142 DOI: 10.1053/j.gastro.2017.04.006]

10 **Rex DK**, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 1997; **112**: 24-28 [PMID: 8978338]

11 **Brown SR**, Baraza W, Din S, Riley S. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. *Cochrane Database Syst Rev* 2016; **4**: CD006439 [PMID: 27056645 DOI: 10.1002/14651858.CD006439.pub4]

12 **Adler A**, Pohl H, Papanikolaou IS, Abou-Rebyeh H, Schachschal G, Veltzke-Schlieker W, Khalifa AC, Setka E, Koch M, Wiedenmann B, Rösch T. A prospective randomised study on narrow-band imaging versus conventional colonoscopy for adenoma detection: does narrow-band imaging induce a learning effect? *Gut* 2008; **57**: 59-64 [PMID: 17681999 DOI: 10.1136/gut.2007.123539]

13 **Adler A**, Aschenbeck J, Yenerim T, Mayr M, Aminalai A, Drossel R, Schröder A, Scheel M, Wiedenmann B, Rösch T. Narrow-band versus white-light high definition television endoscopic imaging for screening colonoscopy: a prospective randomized trial. *Gastroenterology* 2009; **136**: 410-416.e1; quiz 715 [PMID: 19014944 DOI: 10.1053/j.gastro.2008.10.022]

14 **Subramanian V**, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 2011; **43**: 499-505 [PMID: 21360420 DOI: 10.1055/s-0030-1256207]

15 **Gralnek IM**, Siersema PD, Halpern Z, Segol O, Melhem A, Suissa A, Santo E, Sloyer A, Fenster J, Moons LM, Dik VK, D'Agostino RB Jr, Rex DK. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. *Lancet Oncol* 2014; **15**: 353-360 [PMID: 24560453 DOI: 10.1016/S1470-2045(14)70020-8]

16 **Hassan C**, Senore C, Radaelli F, De Pretis G, Sassatelli R, Arrigoni A, Manes G, Amato A, Anderloni A, Armelao F, Mondardini A, Spada C, Omazzi B, Cavina M, Miori G, Campanale C, Sereni G, Segnan N, Repici A. Full-spectrum (FUSE) versus standard forward-viewing colonoscopy in an organised colorectal cancer screening programme. *Gut* 2016; Epub ahead of print [PMID: 27507903 DOI: 10.1136/gutjnl-2016-311906]

17 **Papanikolaou IS**, Apostolopoulos P, Tziatzios G, Vlachou E, Sioulas AD, Polymeros D, Karameris A, Panayiotides I, Alexandrakis G, Dimitriadis GD, Triantafyllou K. Lower adenoma miss rate with FUSE vs. conventional colonoscopy with proximal retroflexion: a randomized back-to-back trial. *Endoscopy* 2017; **49**: 468-475 [PMID: 28107765 DOI: 10.1055/s-0042-124415]

18 **Waye JD**, Heigh RI, Fleischer DE, Leighton JA, Gurudu S, Aldrich LB, Li J, Ramrakhiani S, Edmundowicz SA, Early DS, Jonnalagadda S, Bresalier RS, Kessler WR, Rex DK. A retrograde-viewing device improves detection of adenomas in the colon: a prospective efficacy evaluation (with videos). *Gastrointest Endosc* 2010; **71**: 551-556 [PMID: 20018280 DOI: 10.1016/j.gie.2009.09.043]

19 **Leufkens AM**, DeMarco DC, Rastogi A, Akerman PA, Azzouzi K, Rothstein RI, Vleggaar FP, Repici A, Rando G, Okolo PI, Dewit O, Ignjatovic A, Odstrcil E, East J, Deprez PH, Saunders BP, Kalloo AN, Creel B, Singh V, Lennon AM, Siersema PD; Third Eye Retroscope Randomized Clinical Evaluation [TERRACE] Study Group. Effect of a retrograde-viewing device on adenoma detection rate during

colonoscopy: the TERRACE study. *Gastrointest Endosc* 2011; **73**: 480-489 [PMID: 21067735 DOI: 10.1016/j.gie.2010.09.004]

20 **Desai M**, Sanchez-Yague A, Choudhary A, Pervez A, Gupta N, Vennalaganti P, Vennelaganti S, Fugazza A, Repici A, Hassan C, Sharma P. Impact of cap-assisted colonoscopy on detection of proximal colon adenomas: systematic review and meta-analysis. *Gastrointest Endosc* 2017; **86**: 274-281.e3 [PMID: 28365356 DOI: 10.1016/j.gie.2017.03.1524]

21 **Mir FA**, Boumitri C, Ashraf I. Matteson-Kome ML, Douglas L. Nguyen DL, Puli SR, Bechtold ML. MO1007 Cap-Assisted Colonoscopy Versus Standard Colonoscopy: Is the Cap Beneficial? A Meta-Analysis of Randomized Controlled Trials. *Gastrointest Endosc* 2016; **83**: AB424-AB425 [DOI: 10.1016/j.gie.2016.03.518]

22 **Dik VK**, Gralnek IM, Segol O, Suissa A, Belderbos TD, Moons LM, Segev M, Domanov S, Rex DK, Siersema PD. Multicenter, randomized, tandem evaluation of EndoRings colonoscopy--results of the CLEVER study. *Endoscopy* 2015; **47**: 1151-1158 [PMID: 26220283 DOI: 10.1055/s-0034-1392421]

23 **Biecker E**, Floer M, Heinecke A, Ströbel P, Böhme R, Schepke M, Meister T. Novel endocuff-assisted colonoscopy significantly increases the polyp detection rate: a randomized controlled trial. *J Clin Gastroenterol* 2015; **49**: 413-418 [PMID: 24921209 DOI: 10.1097/MCG.0000000000000166]

24 **Floer M**, Biecker E, Fitzlaff R, Röming H, Ameis D, Heinecke A, Kunsch S, Ellenrieder V, Ströbel P, Schepke M, Meister T. Higher adenoma detection rates with endocuff-assisted colonoscopy - a randomized controlled multicenter trial. *PLoS One* 2014; **9**: e114267 [PMID: 25470133 DOI: 10.1371/journal.pone.0114267]

25 **van Doorn SC**, van der Vlugt M, Depla A, Wientjes CA, Mallant-Hent RC, Siersema PD, Tytgat K, Tuynman H, Kuiken SD, Houben G, Stokkers P, Moons L, Bossuyt P, Fockens P, Mundt MW, Dekker E. Adenoma detection with Endocuff colonoscopy versus conventional colonoscopy: a multicentre randomised controlled trial. *Gut* 2017; **66**: 438-445 [PMID: 26674360 DOI: 10.1136/gutjnl-2015-310097]

26 **Halpern Z**, Gross SA, Gralnek IM, Shpak B, Pochapin M, Hoffman A, Mizrahi M, Rochberger YS, Moshkowitz M, Santo E, Melhem A, Grinshpon R, Pfefer J, Kiesslich R. Comparison of adenoma detection and miss rates between a novel balloon colonoscope and standard colonoscopy: a randomized tandem study. *Endoscopy* 2015; **47**: 238-244 [PMID: 25704662 DOI: 10.1055/s-0034-1391437]

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REVIEW

Ampullary cancer of intestinal origin and duodenal cancer - A logical clinical and therapeutic subgroup in periampullary cancer

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Abstract

Periampullary cancers include pancreatic, ampullary, biliary and duodenal cancers. At presentation, the majority of periampullary tumours have grown to involve the pancreas, bile duct, ampulla and duodenum. This can result in difficulty in defining the primary site of origin in all but the smallest tumors due to anatomical proximity and architectural distortion. This has led to variation in the reported proportions of resected periampullary cancers. Pancreatic cancer is the most common cancer resected with a pancreaticoduodenectomy followed by ampullary

(16%-50%), bile duct (5%-39%), and duodenal cancer (3%-17%). Patients with resected duodenal and ampullary cancers have a better reported median survival (29-47 mo and 22-54 mo) compared to pancreatic cancer (13-19 mo). The poorer survival with pancreatic cancer relates to differences in tumour characteristics such as a higher incidence of nodal, neural and vascular invasion. While small ampullary cancers can present early with biliary obstruction, pancreatic cancers need to reach a certain size before biliary obstruction ensues. This larger size at presentation contributes to a higher incidence of resection margin involvement in pancreatic cancer. Ampullary cancers can be subdivided into intestinal or pancreatobiliary subtype cancers with histomolecular staining. This avoids relying on histomorphology alone, as even some poorly differentiated cancers preserve the histomolecular profile of their mucosa of origin. Histomolecular profiling is superior to anatomic location in prognosticating survival. Ampullary cancers of intestinal subtype and duodenal cancers are similar in their intestinal origin and form a logical clinical and therapeutic subgroup of periampullary cancers. They respond to 5-FU based chemotherapeutic regimens such as capecitabine-oxaliplatin. Unlike pancreatic cancers, *KRAS* mutation occurs in only approximately a third of ampullary and duodenal cancers. Future clinical trials should group ampullary cancers of intestinal origin and duodenal cancers together given their similarities and their response to fluoropyrimidine therapy in combination with oxaliplatin. The addition of anti-epidermal growth factor receptor therapy in this group warrants study.

Key words: Periampullary cancer; Pancreatobiliary subtype; Intestinal subtype; Ampullary cancer; Duodenal cancer; Epidermal growth factor receptor; Pancreatic cancer; Chemotherapy; Pancreaticoduodenectomy; KRAS

Core tip: Periampullary cancers include pancreatic, ampullary, bile duct and duodenal cancers. Pancreatic cancer is the most common cancer resected with a pancreaticoduodenectomy followed by ampullary, bile duct and duodenal cancer. Patients with resected duodenal and ampullary cancers have better prognosis compared to pancreatic cancer. Ampullary cancers can be subdivided into intestinal or pancreatobiliary subtype cancers with histomolecular staining. Histomolecular profiling is superior to anatomic location in prognosticating survival. Ampullary cancers of intestinal subtype and duodenal cancers are similar in their intestinal origin and form a logical clinical and therapeutic subgroup. They respond to 5-FU based chemotherapeutic regimens such as capecitabine-oxaliplatin.

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INTRODUCTION

Periampullary cancers are defined as cancers arising within 2 cm of the papilla of Vater and include pancreatic, ampullary, biliary and duodenal cancers[1]. The region of the ampulla is anatomically complex because it is the area of convergence of the bile duct, pancreatic duct and the duodenum. Conceptually the distinction between pancreatic, biliary, ampullary and duodenal carcinoma is straightforward. The 7th edition 2009 AJCC staging manual states that this distinction is based solely on the presumed anatomical primary site of origin[2]. However, in practice by the time of presentation, the majority of periampullary tumours have grown to involve the pancreas, bile duct, ampulla and duodenum. Therefore it may be difficult to define the primary site of origin in all but the smallest tumors[3]. As a result the distinction between many non-pancreatic periampullary cancers arising in this region from pancreatic cancer is inherently difficult and subjective[4]. This has led to variation in the reported proportions of pancreatic, ampullary, biliary and duodenal cancers resected with a pancreaticoduodenectomy (PD)[5]. Pancreatic cancers represent the majority of cancers resected with a PD in most series[6]. There are fundamental genomic and molecular differences in the four cancer subtypes[7]. There is a need to categorise these cancer subtypes in order to treat them in a way that respects their histological, molecular and behavioural differences.

PROPORTION OF PERIAMPULLARY CANCER SUBTYPES RESECTED WITH A PD

Pancreatic cancer accounts for the majority of periampullary cancers resected with a PD in most series, followed by ampullary 16%-50%, biliary 5%-39%, and duodenal cancer 3%-17%[6-8] (Table 1). The wide variation in the reported incidence and proportion of resected periampullary cancers relates partly to difficulties in accurate determination of the primary tissue origin. This is due to close anatomical proximity of the cancer subtypes and architectural distortion at time of presentation.

Review of pathology slides results in reassignment of cancer origin in a significant number of cases and highlights the importance of central pathology review in clinical trials[9-12]. The Pomianowska *et al*[13] study of 207 resected periampullary cancers, demonstrated that slide review changed the diagnosis in 27% of cases. Inaccurate subtyping of periampullary cancers or the addition of non-pancreatic cancers to pancreatic cancer studies can distort and may inflate survival data and skew tumour size and stage. Indeed, Verbeke *et al*[5]

Table 1 Proportion of periampullary cancer subtypes resected in pancreaticoduodenectomy series

Study (Institution, author, yr)	*n*	Pancreatic cancer	Ampullary cancer	Biliary cancer	Duodenal cancer
Johns Hopkins, United States He *et al*[14], 2014	2564	66%	16%	12%	6%
Academic Medical Centre, The Netherlands Tol *et al*[8], 2015	760	46%	30%	20%	4%
Taipei Veterans General Hospital, Taiwan Chen *et al*[15], 2013	501	34%	50%	10%	5%
Ohio State University, United States Hatzaras *et al*[24], 2010	346	72%	23%	5%	0
Oslo University Hospital, Norway Pomianowska *et al*[16], 2013	207	33%	28%	14%	25%
South Australian Pathology Database, Adelaide, Australia Chandrasegaram *et al*[6], 2015	115	55%	28%	15%	3%
University Medical Center Groningen, The Netherlands Van Roest *et al*[25], 2008	121	42%	25%	16%	17%
Leeds Teaching Hospitals NHS Trust, United Kingdom Menon *et al*[76], 2009	83	33%	29%	39%	N/I
Queen Elizabeth Hospital, Birmingham, United Kingdom Jarufe *et al*[28], 2004	251	53%	35%	12%	N/I
University of California San Diego, United States Katz *et al*[17], 2004	120	62%	26%	8%	4%

N/I: May not have been included.

proposed that the failure to accurately distinguish the cancer subtypes represented the most important factor in the variation in clinicopathological and survival data in periampullary cancer studies.

DIFFERENCES IN SURVIVAL IN PERIAMPULLARY CANCERS

Pancreatic cancer has the poorest survival amongst periampullary cancers. Reported median survival for each cancer subgroup is outlined in Table 2. He *et al*[14] study of 2564 patients with resected periampullary cancers from Johns Hopkins, reported that patients with duodenal cancer had the highest estimated 5-year survival (49%), followed by ampullary cancer (45%), distal bile duct cancer (27%), and pancreatic cancer (18%)[14]. The recent Dutch study by Tol *et al*[8] of 760 cancer resections reported that duodenal cancer patients had the most favourable survival. In the Taiwanese study of 501 patients with periampullary cancer, Chen *et al*[15] reported that patients with ampullary cancer formed the majority (76%) of long-term ($\geqslant$ 5 years) survivors.

DIFFERENCES IN NODAL, NEUROVASCULAR AND MARGIN STATUS IN PERIAMPULLARY CANCERS

The poorer survival seen with pancreatic cancer has been attributed to differences in tumour behavior and invasiveness[6,16-18]. Pancreatic cancers have a higher incidence of nodal, neural and vascular invasion compared to non-pancreatic periampullary cancers[19-25]. Pancreatic cancers also tend to have a much higher incidence of margin positivity[14,22,26,27]. Multiple studies have demonstrated that resection margin status, neurovascular invasion, lymph node involvement and lymph node ratio > 0.2 are important prognostic factors for survival with periampullary adenocarcinomas[8,28,29].

Zenali *et al*[30], showed that patients with duodenal and ampullary cancer had lower frequencies of nodal metastasis, margin involvement and had improved survival compared to patients with pancreatic cancer. Interestingly such differences were not demonstrated between patients with ampullary and duodenal cancers.

Historically periampullary tumours have been treated as a single group. There is strong evidence that non-pancreatic periampullary cancers require further stratification in future clinical trials[7,31].

AMPULLARY CANCER SUBTYPES: INTESTINAL AND PANCREATOBILIARY SUBTYPES

The ampulla of Vater is made up of the union of 2 distinct mucosal tissue types, by virtue of its location at the opening of the bile duct into the duodenum. The ampullo-duodenal part of the papilla is lined by intestinal mucosa and the deeper part of the ampulla is lined by pancreatobiliary ductal mucosa. In 1994 Kimura *et al*[32] classified ampullary cancers into two histological subtypes of either intestinal or pancreatobiliary subtype. Differentiating ampullary cancers into these subtypes is aided by the use of histomolecular staining. This method of subtyping ampullary cancers can overcome difficulties in distinguishing these cancers on the basis of histomorphology alone, as even poorly differentiated cancers preserve the histological marker profile of their mucosa of origin[33].

Table 2 Median survival of patients following resection of periampullary cancers

Study (Institution, author, yr)	*n*	Median survival, mo			
		Pancreatic cancer	Ampullary cancer	Biliary cancer	Duodenal cancer
Johns Hopkins, United States He *et al*[14], 2014	2564	19	47	23	54
Academic Medical Centre, The Netherlands Tol *et al*[8], 2015	760	19	36	29	Not reached
Taipei Veterans General Hospital, Taiwan Chen *et al*[15], 2013	501	13.7	28.9	24.4	21.7
Ohio State University, United States Hatzaras *et al*[24], 2010	346	17.1	44.3	17.9	N/I
Queen Elizabeth Hospital, Birmingham, United Kingdom Jarufe *et al*[28], 2004	251	13.4	35.5	16	N/I

N/I: Subtype not included or reported.

Transcription factor CDX2 is expressed in the nucleus of intestinal epithelium[34,35]. Mucin (MUC) 1 is expressed at the apical border of cells of pancreatobiliary ductal origin[36]. In addition to CDX2 and MUC 1, other markers have been used to subtype ampullary cancers. CDX2, CK 20 and MUC 2 are expressed in intestinal subtype cancers, whereas CK 7, CK 17, MUC 1 and MUC 4 are expressed in pancreatobiliary subtype cancers[37].

The markers have varying sensitivity and specificity in tissue subtyping and often their reported performance depends more on the gold standard to which they are compared to than the clinical utility of the markers[38]. For example, if a very rigid definition is applied so that the term ampullary carcinoma only applies to tumours in which there is absolute certainty of origin from the ampullary epithelium (usually very small tumours centred exquisitely on the ampulla of Vater), then ampullary carcinomas can be expected to be essentially uniformly CDX2 positive and MUC 1 negative. That is, the CDX2 positive, MUC 1 negative profile would be highly sensitive for ampullary carcinoma in this subgroup which, are not difficult to classify as ampullary by a conventional anatomic approach. However, if a more liberal interpretation is applied so that larger tumours which probably, possibly or potentially originally arose from the ampullary epithelium are considered ampullary, then the CDX2 positive, MUC 1 negative profile becomes much less specific for ampullary carcinoma both because larger tumours may lose differentiation and because this expanded subgroup must include at least some tumours which originally arose from the pancreas and merely mimic ampullary carcinoma. This is problematic because it is exactly these anatomically difficult to classify tumours in which ancillary markers would be most useful clinically. Therefore a more sensible approach to the investigation of ancillary markers of ampullary status is to not compare their expression to the older anatomical classification (which is known to be flawed) but to compare their expression to outcome or response to therapy.

For example, Chang *et al*[12] subdivided anatomical periampullary cancers based on protein expression and immunohistochemistry to distinct cancer subtypes. In their study of 208 ampullary cancers, 74% were intestinal subtype (CDX2 +ve, MUC1-ve), and 22% were pancreatobiliary subtype (CDX2 -ve, MUC 1 +ve).

The Chang study demonstrated that patients with pancreatobiliary subtype cancers have poorer survival compared with those with intestinal subtype cancers consistent with historical studies[39-41]. The Schueneman *et al*[42] study of 163 ampullary cancers validated the prognostic role of the histomolecular results of Chang *et al*[12], using MUC 1 and CDX2. In their study, 25% of their patients had pancreatobiliary subtype tumours. These patients had significantly poorer median overall survival of 21.1 mo compared to patients with intestinal subtype tumours, 108.3 mo ($P < 0.0001$)[42].

In the Schiergens retrospective study of their prospective database, patients with pancreatobiliary subtype cancers receiving adjuvant gemcitabine had improved overall survival (32 mo *vs* 13 mo, $P = 0.013$) unlike patients with intestinal subtype cancers who tended to have poorer survival with gemcitabine (35 mo *vs* 112 mo, $P = 0.193$)[39]. This suggests patients with pancreatobiliary subtype cancers may benefit from gemcitabine.

Similarly Leo *et al*[3] demonstrated significantly higher pathological stage and worse overall survival in pancreatic compared to intestinal phenotype ampullary carcinomas. In a more recent study of 510 patients undergoing PD, histopathologic phenotype was superior to tumour anatomic location in prognosticating survival. There was no difference in survival between pancreatobiliary subtype cancers and pancreatic cancer (33.3 mo *vs* 31.4 mo, $P = 0.66$)[43].

Whilst these studies emphasize the clinical outcome differences between pancreatobiliary phenotype and intestinal phenotype ampullary carcinomas, at the genomic level these tumours show both similarities and differences. Yachida *et al*[44] reported whole exome sequencing in a cohort of Japanese and American patients with ampullary cancers. While ampullary cancers were found to be similar to colorectal cancers, and pancreatobiliary subtype cancers

similar to pancreatic cancer, the two subtypes also share similar mutational patterns and signatures differentiating them from colorectal and pancreatic cancers. The authors found tumour suppressor gene ELF3, to be a significant driver of ampullary cancers present in both histological subtypes[44].

Gingras *et al*[45] evaluated 98 ampullary adenocarcinomas, comparing these to 44 distal bile duct and 18 duodenal adenocarcinomas. Mutations in the WNT signaling pathway occurred in approximately half and ELF3 approximately 10% of patients across all three tumour types[45].

A LOGICAL SUBGROUP: AMPULLARY CANCERS OF INTESTINAL SUBTYPE AND DUODENAL CANCERS

Ampullary cancers of intestinal subtype and duodenal cancers are similar in their intestinal origin and form a logical clinical and therapeutic subgroup of periampullary cancers. While *KRAS* mutation occurs in over 90% of pancreatic cancers, both these cancers have a much lower incidence of *KRAS* mutation[7,46].

Valsangkar *et al*[11] reported the incidence of *KRAS* mutation in 75 patients with ampullary cancer was 33%. This was supported by the Kwon *et al*[47] study of 62 ampullary cancers revealing a similar 31% incidence of *KRAS* mutation.

Mikhitarian *et al*[48] analysed the incidence of *KRAS* mutation by ampullary cancer subtype. They reported that 52% of 25 intestinal subtype cancers and 42% of 24 pancreatobiliary subtype cancers had *KRAS* mutation. In the Hechtman *et al*[49] study of 18 pancreatobiliary subtype cancers and 14 intestinal subtype cancer, there was an increased frequency of *KRAS* mutation in the pancreatobiliary subtype cancers (61% *vs* 29%).

While small bowel cancers are rare, the duodenum represents the most common site (56%) for adenocarcinoma of the small bowel, followed by the jejunum (16%) and ileum (13%)[50,51].

As with ampullary cancers, the incidence of *KRAS* mutation is much lower in duodenal cancers compared to pancreatic cancer. Fu *et al*[52] reported the incidence of *KRAS* mutations to be 35% in 78 duodenal cancers.

Given ampullary and duodenal cancers have a much lower incidence of *KRAS* mutation compared to pancreatic cancer, the addition of anti-epidermal growth factor receptor (EGFR) treatment in the metastatic and advanced disease may well be a fruitful area of study on the basis of the morphological and biological similarity to KRAS wild type colorectal adrenocarcinoma where the benefits of this treatment are well proven[53,54].

ADJUVANT STUDIES IN PERIAMPULLARY CANCERS

Historically, non-pancreatic periampullary cancers have been included in trials of pancreatic cancer[55]. In a summary of eleven of the most important randomized controlled trials of adjuvant trials in pancreatic cancer, 4 studies deliberately included non-pancreatic cancers. In most studies, shortcomings in pathological assessment and the lack of standardized pathology to determine the tissue of origin of these cancers may have led to the unintentional inclusion of non-pancreatic cancers[56].

In the ESPAC-3 periampullary cancer trial, 428 patients with periampullary cancer; 297 with ampullary cancers, 96 with bile duct cancers, and 35 with other cancers were randomized to either observation (n = 144) or 6 mo of 5-FU and Folinic acid (n = 143) or gemcitabine (n = 141). There was no survival benefit from adjuvant treatment. However, after adjusting for age, bile duct cancer, poor tumour differentiation and lymph node involvement, on multiple regression analysis there was a survival benefit for chemotherapy compared to observation with a HR of 0.75 (95%CI: 0.57-0.98, P = 0.03)[57].

A recent meta-analysis of 1671 patients reported no survival benefit for adjuvant chemotherapy or chemoradiotherapy in the management of periampullary cancer[58]. The median 5-year survival was 40.0% with adjuvant treatment *vs* 37.5% in the control group with a HR of 1.08 (95%CI: 0.91-1.28; P = 0.067).

Interestingly, the recent UK BILCAP study has shown a benefit for adjuvant capecitabine in bile duct cancers. Of the 447 patients in the study, 156 (35%) had extrahepatic bile duct cancers which would include distal bile duct cancers resected with a PD. In the per-protocol analysis, median survival with capecitabine was 53 mo (95%CI 40-not reached) compared to 36 mo with observation (95%CI: 30-44), HR = 0.75 (95%CI: 0.58-0.97, P = 0.028)[59].

Duodenal cancer studies are often reported with other small bowel cancers, including those arising from the jejunum and ileum. Halfdanarson *et al*[60] in a retrospective review of 491 small bowel adenocarcinomas (57% duodenum; 29% jejunum, 10% ileum) reported a median overall survival of 20.1 mo. Adjuvant therapy did not improve survival in their study. In the Khan *et al*[61] study of 48 resected small bowel adenocarcinomas (63% duodenum, 21% jejunum, 15% ileum), 56% received adjuvant chemotherapy. Adjuvant therapy again did not improve survival in their study.

In the study by Overman *et al*[62] of 54 resected small bowel adenocarcinomas (67% duodenum, 20% jejunum, ileum 13%) although there was no improvement in overall survival with adjuvant chemotherapy, on multivariate analysis, adjuvant therapy improved disease-free survival (HR = 0.27; 95%CI: 0.07-0.98, P = 0.05)[62].

In a more recent National Cancer Database study (NCDB), patients with resected small bowel adenocarcinoma who received adjuvant chemotherapy (n = 1674) were compared to those undergoing surgery alone (n = 3072). This study found that adjuvant chemotherapy improved survival in patients with AJCC stage Ⅲ disease (Median OS 42.4 mo *vs* 26.1 mo; P <

0.001)[63]. The addition of radiotherapy did not improve survival in another adjuvant NCDB study of duodenal adenocarcinoma patients[64].

The role of adjuvant chemotherapy in small bowel adenocarcinomas will be investigated in the international phase Ⅲ study (the BALLAD study) promoted by the International Rare Cancer Initiative[65].

SYSTEMIC CHEMOTHERAPY IN ADVANCED AND METASTATIC AMPULLARY AND DUODENAL CANCER

Several studies have investigated the role of chemotherapy in the advanced or metastatic setting[66-68]. Response rates in ampullary and small intestinal cancers with chemotherapy alone vary between 10%-50%.

A retrospective study of 905 resected periampullary cancers, reported fluoropyrimidine-based chemotherapy was superior to gemcitabine-based chemotherapy in prolonging time to progression in metastatic ampullary cancer suggesting it is a more appropriate first-line approach for ampullary cancers[69].

Overman *et al*[70] achieved an overall response rate (complete response and partial response) of 50% (95%CI: 31%-69%) in their phase II study of capecitabine and Oxaliplatin (CAPOX) for advanced or metastatic ampullary and small intestinal adenocarcinoma[70]. Patients with intestinal adenocarcinoma (n = 18) had a response rate of 61% (95%CI: 36-83%) and those with ampullary adenocarcinoma (n = 12) a response rate of 33% (95%CI: 10%-65%). The poorer response rates in the ampullary compared to the intestinal cancers in this study was thought to be due to the inclusion of ampullary adenocarcinomas of pancreatobiliary origin which may be less responsive to CAPOX.

In the study by Khan *et al*[61], 46/59 (78%) patients received systemic chemotherapy for relapsed, unresectable or metastatic small bowel adenocarcinoma (68% duodenum, 19% jejunum, 14% ileum). Of these, 40 were evaluable for response with a response rate of 50% (1 Complete response, 19 Partial response). The overall 1 year survival was better with chemotherapy 60.9% (95%CI: 45.8-76.0) *vs* 27.3% (P = 0.042). Of the 23 patients who received triplet chemotherapy, 13 received EOX (Epirubicin, Oxaliplatin and Capecitabine) and 4 received ECF (Epirubicin, Cisplatin and 5-FU). Of the 18 patients on doublet chemotherapy, 6 received CAPOX, 4 received FOLFOX (5-FU and oxaliplatin), 3 received FOLFIRI (5-FU and irinotecan) and 3 received capecitabine with Mitomycin C[61].

In a large multicentre retrospective series of different chemotherapy regimens in small bowel cancers, 38 patients received FOLFOX with a tumour response rate of 34% and 11 patients received FOLFIRI with a response rate of 9%. The authors concluded that FOLFOX is the most effective platinum-based chemotherapy for small bowel cancers[71].

From these studies, the combination of a fluoropyrimidine-regimen and oxaliplatin such as FOLFOX or CAPOX appears to be an active regimen in both ampullary and small bowel cancer (*i.e.*, duodenal cancer) suggesting this is a logical treatment regimen in this subgroup of periampullary cancers.

ANTI-EGFR TREATMENT

The lower incidence of *KRAS* mutation in both ampullary and duodenal cancer suggest a potential role for anti-EGFR therapy trials in this subgroup[72]. In the phase II study of panitumumab in KRAS wild-type metastatic adenocarcinoma of the small bowel and ampulla, 9 patients (1 ampullary - pancreatobiliary subtype, 3 duodenal, 5 jejunal/ileal) received panitumumab with minimal clinical activity. This was thought to relate to these tumours being of foregut origin, given the recent findings of less benefit with anti-EGFR therapy in right sided colon cancers compared to left sided cancers[73].

Santini *et al*[74] reported the use of anti-EGFR treatment with Cetuximab in advanced duodenal (n = 2) and jejunal (n = 2) cancers. Cetuximab was associated with CPT-11-based chemotherapy in first-line (2 patients) or second-line (2 patients) therapy for metastatic disease. The patients previously treated had progressed on Folfiri. One patient had a complete response, 2 patients had a partial response and one had stable disease.

While targeted therapy against anti-EGFR pathway is not established in advanced small intestinal cancers, studies are currently evaluating the safety and efficacy of these targeted therapies in this group[75,76].

CONCLUSION

Ampullary and duodenal cancer form a significant proportion of cancers resected with a PD. A strong argument can be made that future clinical trials should group ampullary cancers of intestinal origin and duodenal cancers together given their similarities and their response to fluoropyrimidine therapy in combination with oxaliplatin. Furthermore, treatment response should be compared to both established (CDX2 and MUC1) and more investigational biomarkers. The addition of anti-EGFR therapy in this group warrants further study.

REFERENCES

1 **Sarmiento JM**, Nagomey DM, Sarr MG, Farnell MB. Periampullary cancers: are there differences? *Surg Clin North Am* 2001; **81**: 543-555 [PMID: 11459270 DOI: 10.1016/s0039-6109(05)70142-0]

2 **Edge SE**, Byrd DR, Comptom CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual Seventh Edition. New York: Springer, 2010

3 **Leo JM**, Kalloger SE, Peixoto RD, Gale NS, Webber DL, Owen DA, Renouf D, Schaeffer DF. Immunophenotyping of ampullary carcinomata allows for stratification of treatment specific subgroups. *J Clin Pathol* 2016; **69**: 431-439 [PMID: 26500334 DOI: 10.1136/jclinpath-2015-203337]

4 **Bledsoe JR**, Shinagare SA, Deshpande V. Difficult Diagnostic Problems in Pancreatobiliary Neoplasia. *Arch Pathol Lab Med* 2015; **139**: 848-857 [PMID: 26125425 DOI: 10.5858/arpa.2014-0205-RA]

5 **Verbeke CS**, Gladhaug IP. Resection margin involvement and tumour origin in pancreatic head cancer. *Br J Surg* 2012; **99**: 1036-1049 [PMID: 22517199 DOI: 10.1002/bjs.8734]

6 **Chandrasegaram MD**, Chiam SC, Chen JW, Khalid A, Mittinty ML, Neo EL, Tan CP, Dolan PM, Brooke-Smith ME, Kanhere H, Worthley CS. Distribution and pathological features of pancreatic, ampullary, biliary and duodenal cancers resected with pancreaticoduodenectomy. *World J Surg Oncol* 2015; **13**: 85 [PMID: 25890023 DOI: 10.1186/s12957-015-0498-5]

7 **Chandrasegaram MD**, Chen JW, Price TJ, Zalcberg J, Sjoquist K, Merrett ND. Advances in Molecular Pathology and Treatment of Periampullary Cancers. *Pancreas* 2016; **45**: 32-39 [PMID: 26348463 DOI: 10.1097/MPA.0000000000000385]

8 **Tol JA**, Brosens LA, van Dieren S, van Gulik TM, Busch OR, Besselink MG, Gouma DJ. Impact of lymph node ratio on survival in patients with pancreatic and periampullary cancer. *Br J Surg* 2015; **102**: 237-245 [PMID: 25529117 DOI: 10.1002/bjs.9709]

9 **Nitecki SS**, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg* 1995; **221**: 59-66 [PMID: 7826162 DOI: 10.1097/00000658-199501000-00007]

10 **Brown KM**, Tompkins AJ, Yong S, Aranha GV, Shoup M. Pancreaticoduodenectomy is curative in the majority of patients with node-negative ampullary cancer. *Arch Surg* 2005; **140**: 529-532; discussion 532-533 [PMID: 15967899 DOI: 10.1001/archsurg.140.6.529]

11 **Valsangkar NP**, Ingkakul T, Correa-Gallego C, Mino-Kenudson M, Masia R, Lillemoe KD, Fernández-del Castillo C, Warshaw AL, Liss AS, Thayer SP. Survival in ampullary cancer: potential role of different KRAS mutations. *Surgery* 2015; **157**: 260-268 [PMID: 25616942 DOI: 10.1016/j.surg.2014.08.092]

12 **Chang DK**, Jamieson NB, Johns AL, Scarlett CJ, Pajic M, Chou A, Pinese M, Humphris JL, Jones MD, Toon C, Nagrial AM, Chantrill LA, Chin VT, Pinho AV, Rooman I, Cowley MJ, Wu J, Mead RS, Colvin EK, Samra JS, Corbo V, Bassi C, Falconi M, Lawlor RT, Crippa S, Sperandio N, Bersani S, Dickson EJ, Mohamed MA, Oien KA, Foulis AK, Musgrove EA, Sutherland RL, Kench JG, Carter CR, Gill AJ, Scarpa A, McKay CJ, Biankin AV. Histomolecular phenotypes and outcome in adenocarcinoma of the ampulla of vater. *J Clin Oncol* 2013; **31**: 1348-1356 [PMID: 23439753 DOI: 10.1200/JCO.2012.46.8868]

13 **Pomianowska E**, Grzyb K, Westgaard A, Clausen OP, Gladhaug IP. Reclassification of tumour origin in resected periampullary adenocarcinomas reveals underestimation of distal bile duct cancer. *Eur J Surg Oncol* 2012; **38**: 1043-1050 [PMID: 22883964 DOI: 10.1016/j.ejso.2012.07.113]

14 **He J**, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, Choti MA, Hruban RH, Pawlik TM, Wolfgang CL. 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. *HPB* (Oxford) 2014; **16**: 83-90 [PMID: 23472829 DOI: 10.1111/hpb.12078]

15 **Chen SC**, Shyr YM, Wang SE. Longterm survival after pancreaticoduodenectomy for periampullary adenocarcinomas. *HPB* (Oxford) 2013; **15**: 951-957 [PMID: 23472708 DOI: 10.1111/hpb.12071]

16 **Pomianowska E**, Westgaard A, Mathisen Ø, Clausen OP, Gladhaug IP. Prognostic relevance of number and ratio of metastatic lymph nodes in resected pancreatic, ampullary, and distal bile duct carcinomas. *Ann Surg Oncol* 2013; **20**: 233-241 [PMID: 22893118 DOI: 10.1245/s10434-012-2592-z]

17 **Katz MH**, Bouvet M, Al-Refaie W, Gilpin EA, Moossa AR. Non-pancreatic periampullary adenocarcinomas: an explanation for favorable prognosis. *Hepatogastroenterology* 2004; **51**: 842-846 [PMID: 15143931]

18 **Kim K**, Chie EK, Jang JY, Kim SW, Han SW, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW. Prognostic significance of tumour location after adjuvant chemoradiotherapy for periampullary adenocarcinoma. *Clin Transl Oncol* 2012; **14**: 391-395 [PMID: 22551547 DOI: 10.1007/s12094-012-0814-2]

19 **Morris-Stiff G**, Alabraba E, Tan YM, Shapey I, Bhati C, Tanniere P, Mayer D, Buckels J, Bramhall S, Mirza DF. Assessment of survival advantage in ampullary carcinoma in relation to tumour biology and morphology. *Eur J Surg Oncol* 2009; **35**: 746-750 [PMID: 19167859 DOI: 10.1016/j.ejso.2008.10.010]

20 **Balachandran P**, Sikora SS, Kapoor S, Krishnani N, Kumar A, Saxena R, Kapoor VK. Long-term survival and recurrence patterns in ampullary cancer. *Pancreas* 2006; **32**: 390-395 [PMID: 16670621 DOI: 10.1097/01.mpa.0000220864.80034.63]

21 **Sommerville CA**, Limongelli P, Pai M, Ahmad R, Stamp G, Habib NA, Williamson RC, Jiao LR. Survival analysis after pancreatic resection for ampullary and pancreatic head carcinoma: an analysis of clinicopathological factors. *J Surg Oncol* 2009; **100**: 651-656 [PMID: 19722229 DOI: 10.1002/jso.21390]

22 **Winter JM**, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006; **10**: 1199-1210; discussion 1210-1211 [PMID: 17114007 DOI: 10.1016/j.gassur.2006.08.018]

23 **Mayo SC**, Nathan H, Cameron JL, Olino K, Edil BH, Herman JM, Hirose K, Schulick RD, Choti MA, Wolfgang CL, Pawlik TM. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. *Cancer* 2012; **118**: 2674-2681 [PMID: 21935914 DOI: 10.1002/cncr.26553]

24 **Hatzaras I**, George N, Muscarella P, Melvin WS, Ellison EC, Bloomston M. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. *Ann Surg Oncol* 2010; **17**: 991-997 [PMID: 20108122 DOI: 10.1245/s10434-009-0883-9]

25 **van Roest MH**, Gouw AS, Peeters PM, Porte RJ, Slooff MJ, Fidler V, de Jong KP. Results of pancreaticoduodenectomy in patients with periampullary adenocarcinoma: perineural growth more important prognostic factor than tumor localization. *Ann Surg* 2008; **248**: 97-103 [PMID: 18580212 DOI: 10.1097/SLA.0b013e31817b6609]

26 **Verbeke CS**, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. *Br J Surg* 2006; **93**: 1232-1237 [PMID: 16804874 DOI: 10.1002/bjs.5397]

27 **Chandrasegaram MD**, Goldstein D, Simes J, Gebski V, Kench JG, Gill AJ, Samra JS, Merrett ND, Richardson AJ, Barbour AP. Meta-analysis of radical resection rates and margin assessment in pancreatic cancer. *Br J Surg* 2015; **102**: 1459-1472 [PMID: 26350029 DOI: 10.1002/bjs.9892]

28 **Jarufe NP**, Coldham C, Mayer AD, Mirza DF, Buckels JA, Bramhall SR. Favourable prognostic factors in a large UK experience of adenocarcinoma of the head of the pancreas and periampullary region. *Dig Surg* 2004; **21**: 202-209 [PMID: 15218236 DOI: 10.1159/000079346]

29 **Farid SG**, Falk GA, Joyce D, Chalikonda S, Walsh RM, Smith AM, Morris-Stiff G. Prognostic value of the lymph node ratio after resection of periampullary carcinomas. *HPB* (Oxford) 2014; **16**: 582-591 [PMID: 23777362 DOI: 10.1111/j.1477-2574.2012.00614.x]

30 **Zenali M**, Overman MJ, Rashid A, Broaddus RB, Wang H, Katz MH, Fleming JB, Abbruzzese JL, Wang H. Clinicopathologic features and prognosis of duodenal adenocarcinoma and comparison with ampullary and pancreatic ductal adenocarcinoma. *Hum Pathol* 2013; **44**: 2792-2798 [PMID: 24139211 DOI: 10.1016/j.humpath.2013.07.030]

31 **Westgaard A**, Pomianowska E, Clausen OP, Gladhaug IP. Intestinal-type and pancreatobiliary-type adenocarcinomas: how does ampullary carcinoma differ from other periampullary malignancies? *Ann Surg Oncol* 2013; **20**: 430-439 [PMID: 22956064 DOI: 10.1245/s10434-012-2603-0]

32 **Kimura W**, Futakawa N, Yamagata S, Wada Y, Kuroda A, Muto T, Esaki Y. Different clinicopathologic findings in two histologic types of carcinoma of papilla of Vater. *Jpn J Cancer Res* 1994; **85**: 161-166 [PMID: 7511574 DOI: 10.1111/j.1349-7006.1994.tb02077.x]

33 **Fischer HP**, Zhou H. Pathogenesis of carcinoma of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 2004; **11**: 301-309 [PMID: 15549428 DOI: 10.1007/s00534-004-0898-3]

34 **Werling RW**, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin:

an immunohistochemical survey of 476 primary and metastatic carcinomas. *Am J Surg Pathol* 2003; **27**: 303-310 [PMID: 12604886 DOI: 10.1097/00000478-200303000-00003]

35 **Moskaluk CA**, Zhang H, Powell SM, Cerilli LA, Hampton GM, Frierson HF Jr. Cdx2 protein expression in normal and malignant human tissues: an immunohistochemical survey using tissue microarrays. *Mod Pathol* 2003; **16**: 913-919 [PMID: 13679455 DOI: 10.1097/01.mp.0000086073.92773.55]

36 **Lau SK**, Weiss LM, Chu PG. Differential expression of MUC1, MUC2, and MUC5AC in carcinomas of various sites: an immunohistochemical study. *Am J Clin Pathol* 2004; **122**: 61-69 [PMID: 15272531 DOI: 10.1309/9r66-73qe-c06d-86y4]

37 **Kawabata Y**, Tanaka T, Nishisaka T, Inao T, Nishi T, Yano S. Cytokeratin 20 (CK20) and apomucin 1 (MUC1) expression in ampullary carcinoma: Correlation with tumor progression and prognosis. *Diagn Pathol* 2010; **5**: 75 [PMID: 21106111 DOI: 10.1186/1746-1596-5-75]

38 **Kumari N**, Prabha K, Singh RK, Baitha DK, Krishnani N. Intestinal and pancreatobiliary differentiation in periampullary carcinoma: the role of immunohistochemistry. *Hum Pathol* 2013; **44**: 2213-2219 [PMID: 23834763 DOI: 10.1016/j.humpath.2013.05.003]

39 **Schiergens TS**, Reu S, Neumann J, Renz BW, Niess H, Boeck S, Heinemann V, Bruns CJ, Jauch KW, Kleespies A. Histomorphologic and molecular phenotypes predict gemcitabine response and overall survival in adenocarcinoma of the ampulla of Vater. *Surgery* 2015; **158**: 151-161 [PMID: 25819575 DOI: 10.1016/j.surg.2015.02.001]

40 **Roh YH**, Kim YH, Lee HW, Kim SJ, Roh MS, Jeong JS, Jung GJ. The clinicopathologic and immunohistochemical characteristics of ampulla of Vater carcinoma: the intestinal type is associated with a better prognosis. *Hepatogastroenterology* 2007; **54**: 1641-1644 [PMID: 18019683]

41 **Westgaard A**, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, Clausen OP, Gladhaug IP. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. *BMC Cancer* 2008; **8**: 170 [PMID: 18547417 DOI: 10.1186/1471-2407-8-170]

42 **Schueneman A**, Goggins M, Ensor J, Saka B, Neishaboori N, Lee S, Maitra A, Varadhachary G, Rezaee N, Wolfgang C, Adsay V, Wang H, Overman MJ. Validation of histomolecular classification utilizing histological subtype, MUC1, and CDX2 for prognostication of resected ampullary adenocarcinoma. *Br J Cancer* 2015; **113**: 64-68 [PMID: 25989273 DOI: 10.1038/bjc.2015.172]

43 **Williams JL**, Chan CK, Toste PA, Elliott IA, Vasquez CR, Sunjaya DB, Swanson EA, Koo J, Hines OJ, Reber HA, Dawson DW, Donahue TR. Association of Histopathologic Phenotype of Periampullary Adenocarcinomas With Survival. *JAMA Surg* 2017; **152**: 82-88 [PMID: 27732711 DOI: 10.1001/jamasurg.2016.3466]

44 **Yachida S**, Wood LD, Suzuki M, Takai E, Totoki Y, Kato M, Luchini C, Arai Y, Nakamura H, Hama N, Elzawahry A, Hosoda F, Shirota T, Morimoto N, Hori K, Funazaki J, Tanaka H, Morizane C, Okusaka T, Nara S, Shimada K, Hiraoka N, Taniguchi H, Higuchi R, Oshima M, Okano K, Hirono S, Mizuma M, Arihiro K, Yamamoto M, Unno M, Yamaue H, Weiss MJ, Wolfgang CL, Furukawa T, Nakagama H, Vogelstein B, Kiyono T, Hruban RH, Shibata T. Genomic Sequencing Identifies ELF3 as a Driver of Ampullary Carcinoma. *Cancer Cell* 2016; **29**: 229-240 [PMID: 26806338 DOI: 10.1016/j.ccell.2015.12.012]

45 **Gingras MC**, Covington KR, Chang DK, Donehower LA, Gill AJ, Ittmann MM, Creighton CJ, Johns AL, Shinbrot E, Dewal N, Fisher WE; Australian Pancreatic Cancer Genome Initiative, Pilarsky C, Grützmann R, Overman MJ, Jamieson NB, Van Buren G 2nd, Drummond J, Walker K, Hampton OA, Xi L, Muzny DM, Doddapaneni H, Lee SL, Bellair M, Hu J, Han Y, Dinh HH, Dahdouli M, Samra JS, Bailey P, Waddell N, Pearson JV, Harliwong I, Wang H, Aust D, Oien KA, Hruban RH, Hodges SE, McElhany A, Saengboonmee C, Duthie FR, Grimmond SM, Biankin AV, Wheeler DA, Gibbs RA. Ampullary Cancers Harbor ELF3 Tumor Suppressor Gene Mutations and Exhibit Frequent WNT Dysregulation. *Cell Rep* 2016; **14**: 907-919 [PMID: 26804919 DOI: 10.1016/j.celrep.2015.12.005]

46 **Biankin AV**, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu J, Chang DK, Cowley MJ, Gardiner BB, Song S, Harliwong I, Idrisoglu S, Nourse C, Nourbakhsh E, Manning S, Wani S, Gongora M, Pajic M, Scarlett CJ, Gill AJ, Pinho AV, Rooman I, Anderson M, Holmes O, Leonard C, Taylor D, Wood S, Xu Q, Nones K, Fink JL, Christ A, Bruxner T, Cloonan N, Kolle G, Newell F, Pinese M, Mead RS, Humphris JL, Kaplan W, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chou A, Chin VT, Chantrill LA, Mawson A, Samra JS, Kench JG, Lovell JA, Daly RJ, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N; Australian Pancreatic Cancer Genome Initiative, Kakkar N, Zhao F, Wu YQ, Wang M, Muzny DM, Fisher WE, Brunicardi FC, Hodges SE, Reid JG, Drummond J, Chang K, Han Y, Lewis LR, Dinh H, Buhay CJ, Beck T, Timms L, Sam M, Begley K, Brown A, Pai D, Panchal A, Buchner N, De Borja R, Denroche RE, Yung CK, Serra S, Onetto N, Mukhopadhyay D, Tsao MS, Shaw PA, Petersen GM, Gallinger S, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Schulick RD, Wolfgang CL, Morgan RA, Lawlor RT, Capelli P, Corbo V, Scardoni M, Tortora G, Tempero MA, Mann KM, Jenkins NA, Perez-Mancera PA, Adams DJ, Largaespada DA, Wessels LF, Rust AG, Stein LD, Tuveson DA, Copeland NG, Musgrove EA, Scarpa A, Eshleman JR, Hudson TJ, Sutherland RL, Wheeler DA, Pearson JV, McPherson JD, Gibbs RA, Grimmond SM. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012; **491**: 399-405 [PMID: 23103869 DOI: 10.1038/nature11547]

47 **Kwon MJ**, Kim JW, Jung JP, Cho JW, Nam ES, Cho SJ, Kim JS, Park HR, Min SK, Seo J, Min KW, Kim DH, Jeon JY. Low incidence of KRAS, BRAF, and PIK3CA mutations in adenocarcinomas of the ampulla of Vater and their prognostic value. *Hum Pathol* 2016; **50**: 90-100 [PMID: 26997442 DOI: 10.1016/j.humpath.2015.11.009]

48 **Mikhitarian K**, Pollen M, Zhao Z, Shyr Y, Merchant NB, Parikh A, Revetta F, Washington MK, Vnencak-Jones C, Shi C. Epidermal growth factor receptor signaling pathway is frequently altered in ampullary carcinoma at protein and genetic levels. *Mod Pathol* 2014; **27**: 665-674 [PMID: 24186143 DOI: 10.1038/modpathol.2013.185]

49 **Hechtman JF**, Liu W, Sadowska J, Zhen L, Borsu L, Arcila ME, Won HH, Shah RH, Berger MF, Vakiani E, Shia J, Klimstra DS. Sequencing of 279 cancer genes in ampullary carcinoma reveals trends relating to histologic subtypes and frequent amplification and overexpression of ERBB2 (HER2). *Mod Pathol* 2015; **28**: 1123-1129 [PMID: 25975284 DOI: 10.1038/modpathol.2015.57]

50 **Bilimoria KY**, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. *Ann Surg* 2009; **249**: 63-71 [PMID: 19106677 DOI: 10.1097/SLA.0b013e31818e4641]

51 **Gleason D**, Miller-Hammond KE, Gibbs JF. Small Bowel Cancer. In Surgical Oncology. Springer, New York, 2014: 217-234 [DOI: 10.1007/978-1-4939-1423-4_10]

52 **Fu T**, Guzzetta AA, Jeschke J, Vatapalli R, Dave P, Hooker CM, Morgan R, Iacobuzio-Donahue CA, Liu B, Ahuja N. KRAS G>A mutation favors poor tumor differentiation but may not be associated with prognosis in patients with curatively resected duodenal adenocarcinoma. *Int J Cancer* 2013; **132**: 2502-2509 [PMID: 23065691 DOI: 10.1002/ijc.27910]

53 **Lièvre A**, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, Côté JF, Tomasic G, Penna C, Ducreux M, Rougier P, Penault-Llorca F, Laurent-Puig P. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006; **66**: 3992-3995 [PMID: 16618717 DOI: 10.1158/0008-5472.CAN-06-0191]

54 **Peeters M**, Douillard JY, Van Cutsem E, Siena S, Zhang K, Williams R, Wiezorek J. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. *J Clin Oncol* 2013; **31**: 759-765 [PMID: 23182985 DOI: 10.1200/JCO.2012.45.1492]

55 **Kim SM**, Eads JR. Adjuvant and Neoadjuvant Therapy for Resectable Pancreatic and Periampullary Cancer. *Surg Clin North Am* 2016; **96**: 1287-1300 [PMID: 27865278 DOI: 10.1016/j.suc.2016.07.004]

56 **Erdmann JI**, Eskens FA, Vollmer CM, Kok NF, Groot Koerkamp B, Biermann K, van Eijck CH. Histological and Molecular

Subclassification of Pancreatic and Nonpancreatic Periampullary Cancers: Implications for (Neo) Adjuvant Systemic Treatment. *Ann Surg Oncol* 2015; **22**: 2401-2407 [PMID: 25503345 DOI: 10.1245/s10434-014-4267-4]

57 **Neoptolemos JP**, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, Carter R, Tebbutt NC, Dervenis C, Smith D, Glimelius B, Charnley RM, Lacaine F, Scarfe AG, Middleton MR, Anthoney A, Ghaneh P, Halloran CM, Lerch MM, Oláh A, Rawcliffe CL, Verbeke CS, Campbell F, Büchler MW; European Study Group for Pancreatic Cancer. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 2012; **308**: 147-156 [PMID: 22782416 DOI: 10.1001/jama.2012.7352]

58 **Acharya A**, Markar SR, Sodergren MH, Malietzis G, Darzi A, Athanasiou T, Khan AZ. Meta-analysis of adjuvant therapy following curative surgery for periampullary adenocarcinoma. *Br J Surg* 2017; **104**: 814-822 [PMID: 28518410 DOI: 10.1002/bjs.10563]

59 **Primrose JN,** Fox R, Palmer DH, Prasad R, Mirza D, Anthoney DA, Corrie P, Falk S, Wasan HS, Ross PJ, Wall LR. Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study. *J Clin Oncol* 2017; **35**: 4006 [DOI: 10.1200/JCO.2017.35.15_suppl.4006]

60 **Halfdanarson TR**, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. *Am J Surg* 2010; **199**: 797-803 [PMID: 20609724 DOI: 10.1016/j.amjsurg.2009.05.037]

61 **Khan K**, Peckitt C, Sclafani F, Watkins D, Rao S, Starling N, Jain V, Trivedi S, Stanway S, Cunningham D, Chau I. Prognostic factors and treatment outcomes in patients with Small Bowel Adenocarcinoma (SBA): the Royal Marsden Hospital (RMH) experience. *BMC Cancer* 2015; **15**: 15 [PMID: 25603878 DOI: 10.1186/s12885-015-1014-6]

62 **Overman MJ**, Kopetz S, Lin E, Abbruzzese JL, Wolff RA. Is there a role for adjuvant therapy in resected adenocarcinoma of the small intestine. *Acta Oncol* 2010; **49**: 474-479 [PMID: 20397775 DOI: 10.3109/02841860903490051]

63 **Ecker BL**, McMillan MT, Datta J, Mamtani R, Giantonio BJ, Dempsey DT, Fraker DL, Drebin JA, Karakousis GC, Roses RE. Efficacy of adjuvant chemotherapy for small bowel adenocarcinoma: A propensity score-matched analysis. *Cancer* 2016; **122**: 693-701 [PMID: 26717303 DOI: 10.1002/cncr.29840]

64 **Ecker BL**, McMillan MT, Datta J, Lee MK, Karakousis GC, Vollmer CM Jr, Drebin JA, Fraker DL, Roses RE. Adjuvant chemotherapy versus chemoradiotherapy in the management of patients with surgically resected duodenal adenocarcinoma: A propensity score-matched analysis of a nationwide clinical oncology database. *Cancer* 2017; **123**: 967-976 [PMID: 28263387 DOI: 10.1002/cncr.30439]

65 **Keat N**, Law K, Seymour M, Welch J, Trimble T, Lascombe D, Negrouk A. International rare cancers initiative. *Lancet Oncol* 2013; **14**: 109-110 [PMID: 23369681 DOI: 10.1016/S1470-2045(12)70570-3]

66 **Tsushima T**, Taguri M, Honma Y, Takahashi H, Ueda S, Nishina T, Kawai H, Kato S, Suenaga M, Tamura F, Morita S, Boku N. Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. *Oncologist* 2012; **17**: 1163-1170 [PMID: 22622149 DOI: 10.1634/theoncologist.2012-0079]

67 **Zaanan A**, Gauthier M, Malka D, Locher C, Gornet JM, Thirot-Bidault A, Tougeron D, Taïeb J, Bonnetain F, Aparicio T; Association des Gastro Entérologues Oncologues. Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. *Cancer* 2011; **117**: 1422-1428 [PMID: 21425142 DOI: 10.1002/cncr.25614]

68 **Overman MJ**, Kopetz S, Wen S, Hoff PM, Fogelman D, Morris J, Abbruzzese JL, Ajani JA, Wolff RA. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. *Cancer* 2008; **113**: 2038-2045 [PMID: 18759326 DOI: 10.1002/cncr.23822]

69 **Jiang ZQ**, Varadhachary G, Wang X, Kopetz S, Lee JE, Wang H, Shroff R, Katz M, Wolff RA, Fleming J, Overman MJ. A retrospective study of ampullary adenocarcinomas: overall survival and responsiveness to fluoropyrimidine-based chemotherapy. *Ann Oncol* 2013; **24**: 2349-2353 [PMID: 23704197 DOI: 10.1093/annonc/mdt191]

70 **Overman MJ**, Varadhachary GR, Kopetz S, Adinin R, Lin E, Morris JS, Eng C, Abbruzzese JL, Wolff RA. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. *J Clin Oncol* 2009; **27**: 2598-2603 [PMID: 19164203 DOI: 10.1200/JCO.2008.19.7145]

71 **Zaanan A**, Costes L, Gauthier M, Malka D, Locher C, Mitry E, Tougeron D, Lecomte T, Gornet JM, Sobhani I, Moulin V, Afchain P, Taïeb J, Bonnetain F, Aparicio T. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. *Ann Oncol* 2010; **21**: 1786-1793 [PMID: 20223786 DOI: 10.1093/annonc/mdq038]

72 **Raghav K**, Overman MJ. Small bowel adenocarcinomas--existing evidence and evolving paradigms. *Nat Rev Clin Oncol* 2013; **10**: 534-544 [PMID: 23897080 DOI: 10.1038/nrclinonc.2013.132]

73 **Gulhati P**, Raghav KP, Shroff RT, Varadhachary GR, Javle MM, Qiao W, Wang H, Morris J, Wolff RA, Overman MJ. Phase II study of panitumumab in KRAS wild-type metastatic adenocarcinoma of the small bowel or ampulla of vater. *J Clin Oncol* 2017; **35**: published online before print. [DOI: 10.1200/JCO.2017.35.15_suppl.e15799]

74 **Santini D**, Fratto ME, Spoto C, Russo A, Galluzzo S, Zoccoli A, Vincenzi B, Tonini G. Cetuximab in small bowel adenocarcinoma: a new friend? *Br J Cancer* 2010; **103**: 1305; author reply 1306 [PMID: 20842127 DOI: 10.1038/sj.bjc.6605898]

75 **Zaaimi Y**, Aparicio T, Laurent-Puig P, Taieb J, Zaanan A. Advanced small bowel adenocarcinoma: Molecular characteristics and therapeutic perspectives. *Clin Res Hepatol Gastroenterol* 2016; **40**: 154-160 [PMID: 26547136 DOI: 10.1016/j.clinre.2015.09.008]

76 **Menon KV**, Gomez D, Smith AM, Anthoney A, Verbeke CS. Impact of margin status on survival following pancreatoduodenectomy for cancer: the Leeds Pathology Protocol (LEEPP). *HPB* (Oxford) 2009; **11**: 18-24 [PMID: 19590619 DOI: 10.1111/j.1477-2574.2008.00013.x]

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ORIGINAL ARTICLE

Retrospective Study

Clinical outcomes of Clutch Cutter endoscopic submucosal dissection for older patients with early gastric cancer

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Informed consent statement: The ethics committee of Aso Iizuka Hospital approved this study (registration No. 12120). Written informed consent was obtained from all patients.

Conflict-of-interest statement: Kazuya Akahoshi and Hidefumi Akahane (Fujifilm) have applied for a patent in Europe for the CC described in this article. Japan, China, and the United States have already granted patents.

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Abstract

AIM

To evaluate the clinical outcome of endoscopic sub-

mucosal dissection using the Clutch Cutter (ESDCC) in older patients.

METHODS

We reviewed 232 consecutive patients with early gastric cancer who underwent ESDCC between June 2010 and February 2014 at Aso Iizuka Hospital. We divided patients into two groups according to age: Older patients (> 80 years, *n* = 64) and non-older patients (≤ 80 years, *n* = 168). We retrospectively compared the prevalence rates of pre-existing comorbidities, anticoagulant therapy, *en bloc* resection, mean duration of hospitalization, incidence of ESDCC-related complications, change in performance status (PS) before and after ESDCC, and financial cost of admission.

RESULTS

The older group comprised 64 patients with a mean age of 84.1 years, and the non-older group comprised 168 patients with a mean age of 69.5 years. Older patients had significantly more pre-existing comorbidities than did non-older patients, specifically heart disease ($P < 0.05$). The *en bloc* resection rate in non-older patients was significantly higher than that in older patients (100% *vs* 95.3%, $P = 0.02$). There were no significant differences between the older and non-older groups in the incidence of ESDCC-related complications (*i.e.*, postoperative bleeding and perforation) and the post-ESDCC change in PS. There were also no significant differences between the older and non-older groups in the mean duration of hospitalization (11.4 and 10.7 d, respectively) and financial cost of admission (657040 JPY and 574890 JPY, respectively).

CONCLUSION

ESDCC has a good clinical outcome in older patients.

Key words: Older patients; Clutch Cutter; Endoscopic submucosal dissection; Early gastric cancer; Financial cost; Duration of hospitalization

Core tip: No previous reports have described the clinical outcomes of endoscopic submucosal dissection using the Clutch Cutter (ESDCC) for older patients with early gastric cancer (EGC). The present study evaluated the clinical outcomes, including medical economics, associated with ESDCC for older patients. There was no significant difference between older patients and non-older patients in the rate of ESDCC-related complications. There was also no significant difference between older and non-older patients in the mean duration of hospitalization and medical economics. We conclude that ESDCC is safe and effective for older and non-older patients with EGC.

Otsuka Y, Akahoshi K, Yasunaga K, Kubokawa M, Gibo J, Osada S, Tokumaru K, Miyamoto K, Sato T, Shiratsuchi Y, Oya M, Koga H, Ihara E, Nakamura K. Clinical outcomes of Clutch Cutter endoscopic submucosal dissection for older patients with early gastric cancer. *World J Gastrointest Oncol* 2017; 9(10): 416-422 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i10/416.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i10.416

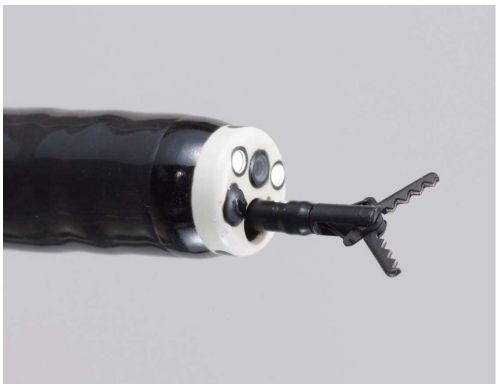

Figure 1 The distal tip of the Clutch Cutter (long type: Blade length of 5 mm).

INTRODUCTION

In an increasingly older society, a growing number of endoscopic treatments are being performed in patients with age-associated comorbidities[1]. Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) has become widely accepted, as it provides *en bloc* resection and histologically complete resection, and it is less invasive than surgical resection[2-5]. ESD recently been reported to be a safe and reliable procedure for treating early gastrointestinal tract cancer in older patients[6-10]. However, there is little information on the medical costs of ESD, the mean duration of hospitalization, and the change in performance status (PS) before and after ESD. Akahoshi and Fujifilm[11] developed a grasping-type scissors forceps [*i.e.*, the "Clutch Cutter" (CC), Fujifilm, Tokyo, Japan, Figure 1] for safe ESD. We previously showed that ESD using the CC (ESDCC) is a safe and effective method for treating patients with early cancer in the esophagus, stomach, duodenum, or colorectum[11-17]. However, no reports have described the clinical outcomes of ESDCC for older patients with EGC. The present study evaluated the clinical outcomes of ESDCC for older patients with EGC, including the medical economics associated with ESDCC.

MATERIALS AND METHODS

Patients

ESDCC was performed in 269 consecutive patients with EGC between June 2010 and February 2014 at Aso Iizuka Hospital. A total of 37 patients were excluded because their post-ESD histological analysis did not meet the clinical indication criteria for ESD proposed by Gotoda *et al*[18] and the Japanese Gastric Cancer Association[19] (*i.e.*, listed in the exclusion criteria group).

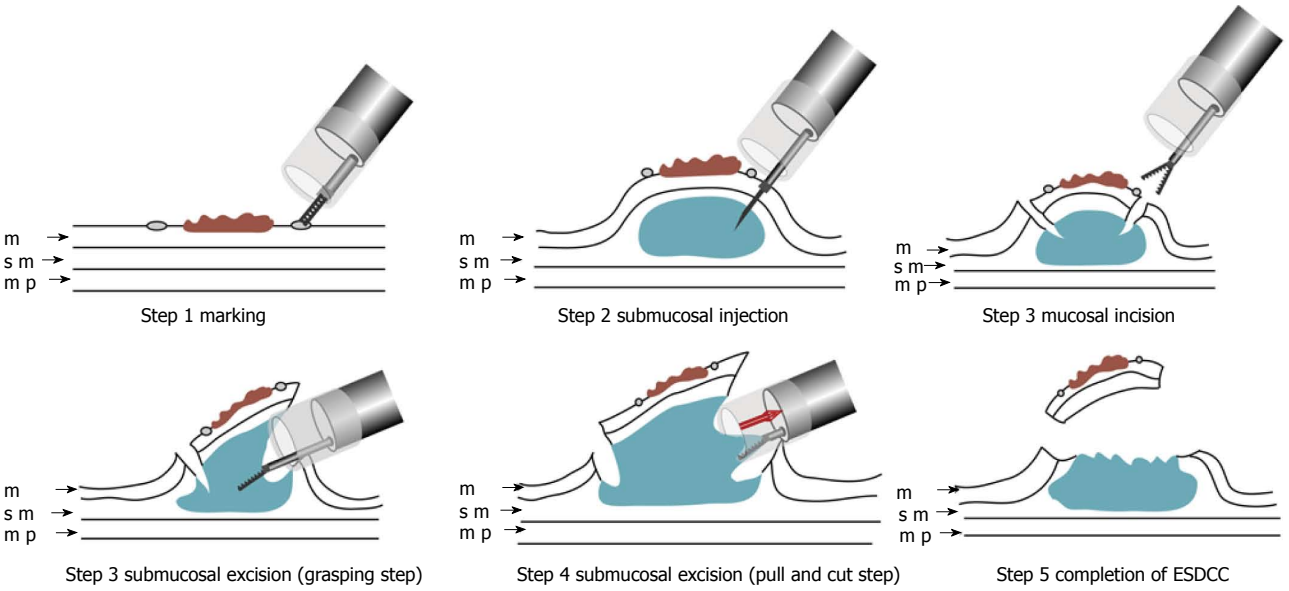

Figure 2 Schema showing endoscopic submucosal dissection using the Clutch Cutter technique. m: Mucosa; sm: Submucosa; mp: Muscularis propria; ESDCC: Endoscopic submucosal dissection using the Clutch Cutter.

A total of 232 consecutive patients with EGC were enrolled in this retrospective study.

We divided the patients into two groups according to age: Older patients (> 80 years, mean age: 84.1 SD ± 3.2 years old) and non-older patients (≤ 80 years, mean age: 69.5 SD ± 7.3 years old). The following factors were retrospectively compared between the two groups: Pre-existing comorbidities, anticoagulant therapy, *en bloc* resection rate, mean duration of hospitalization, incidence of ESDCC-related complications, change in PS before and after ESD, and financial cost of admission. We used a prospectively maintained ESDCC database for the analyses of anticoagulant therapy, *en bloc* resection rate, and incidence of ESDCC-related complications; our institutional medical and accounting records for each patient were used to analyze pre-existing comorbidities, mean duration of hospitalization, change in PS after ESD, and financial cost of admission. PS was classified using the Eastern Cooperative Oncology Group scale. The indication for ESD was a PS score of 0, 1, or 2.

ESD with the Clutch Cutter procedure

Detailed technical procedures of ESDCC have been reported previously[11-17] (Figure 2). ESDCC was conducted using a single-channel therapeutic endoscope (EG-450RD5; Fujifilm) or a two-channel multi-bending endoscope (GIF-2T240M; Olympus, Tokyo, Japan). A long, transparent hood (F-01; Top Co. Ltd., Tokyo, Japan) was attached to the tip of the endoscope to facilitate submucosal dissection by elevating the lesion. Circumferential markings were made using the CC in closed mode. A hyaluronic acid solution (MucoUp; Johnson and Johnson, Tokyo, Japan) with diluted epinephrine (0.0002%) and indigo carmine (0.0002%) was injected into the submucosal layer to lift up the lesion. The target mucosal and submucosal layer tissues were grasped, lifted up, and cut using the CC. Finally, the lesion was completely resected using the CC (Figure 3). When bleeding occurred during the procedure, it was treated *via* coagulation with the CC. The forced coagulation mode (VIO 300D; Erbe, Tübingen, Germany) 30 W (effect 3) was used for marking, the endo cut Q mode (effect 2, duration 3, interval 1) was used for cutting, and the soft coagulation mode 100 W (effect 5) was used for hemostatic treatment.

Statistical analysis

Statistical analyses for comparison between the older and non-older groups was performed using the χ^2-test, the Wilcoxon/Kruskal-Wallis test, and Fisher's exact probability test. The χ^2-test was used to evaluate intergroup differences in anticoagulant therapy and *en bloc* resection, incidence of ESDCC-related complications, and change in PS before and after ESD. The Wilcoxon/Kruskal-Wallis test was used to evaluate intergroup differences in the mean duration of hospitalization and financial cost of admission. Fisher's exact probability test was used to evaluate intergroup differences in pre-existing comorbidities. Differences were considered significant at $P < 0.05$.

RESULTS

Patients' characteristics

The older group comprised 64 patients with a mean age of 84.1 years, and the non-older group comprised 168 patients with a mean age of 69.5 years (Table 1). The two groups significantly differed in terms of age, but not sex. Older patients had a significantly higher rate of pre-existing comorbidities than did non-older patients ($P < 0.05$), especially heart disease. The proportion of the older group receiving anticoagulant therapy was not

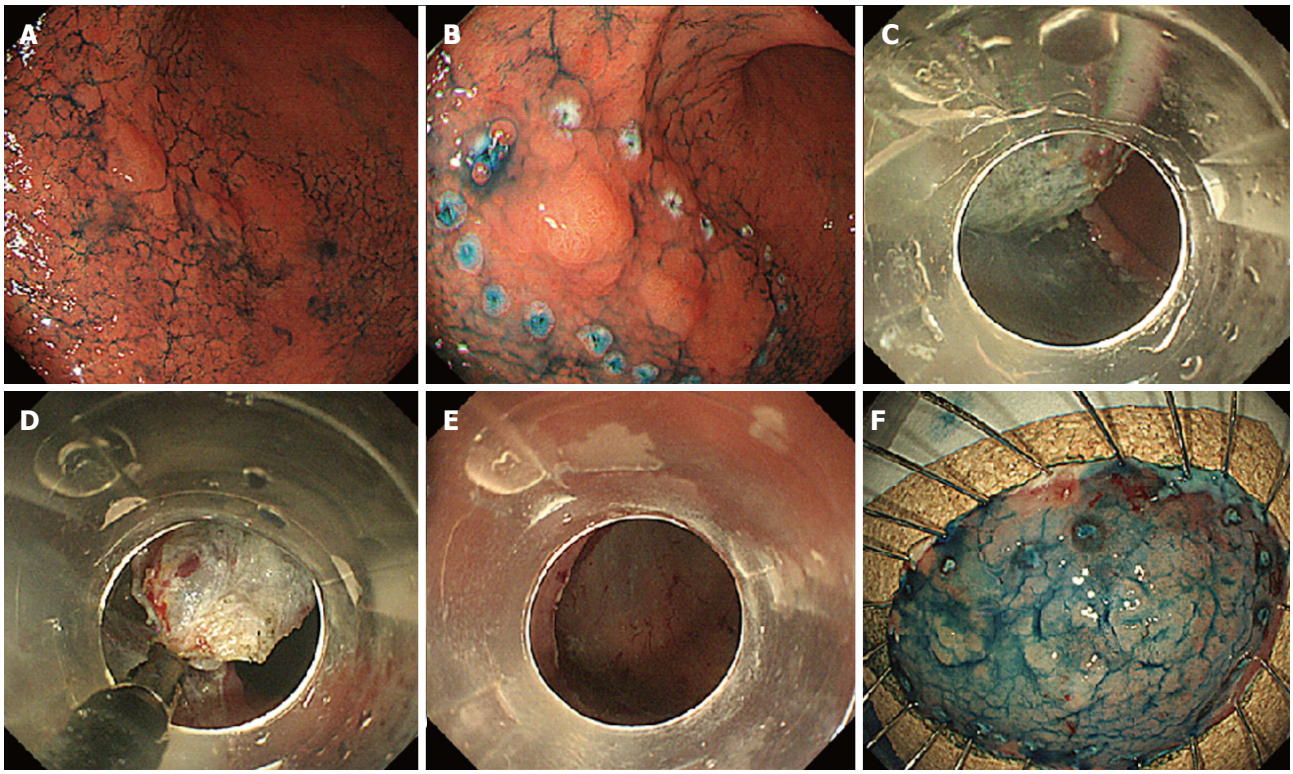

Figure 3 Endoscopic submucosal dissection using the Clutch Cutter in an 82-year-old Japanese male. A: Indigo carmine was sprayed to demarcate the lesion; B: Markings outside the lesion; C and D: The submucosal tissue under the lesion was gradually grasped and dissected from the muscle layer; E: The lesion was completely cut from the muscle layer; F: Fixation of the specimen.

Table 1 Patient characteristics *n* (%)

	Older group (*n* = 64)	Non-older group (*n* = 168)	*P* value
Mean age	84.2	69.5	
Gender ratio (M/F)	44/20	118/50	NS
No. of performance state 3 or 4	5 (7.8)	4 (2.4)	
Pre-existing comorbidity			
Total prevalence rates	58 (90.6)	123 (73.2)	0.0042
Cerebral infarction	11 (17.2)	17 (10.1)	NS
Cardiovascular disease	23 (35.9)	25 (14.9)	0.0004
Respiratory disease	8 (12.5)	12 (7.1)	NS
Chronic renal dysfunction	8 (12.5)	21 (12.5)	NS
Liver cirrhosis	1 (1.6)	12 (7.1)	NS
Diabetes	20 (31.2)	47 (28.0)	NS
Hypertension	44 (68.8)	98 (58.3)	NS
Senile dementia	7 (10.9)	14 (8.3)	NS
Anti-coagulant therapy	4 (6.3)	12 (7.1)	NS

NS: Not significant.

Table 2 Tumors characteristics

	Older group (*n* = 64)	Non-older group (*n* = 168)	*P* value
Location			
Upper	28	39	0.019
Middle	16	55	NS
Lower	20	72	NS
Residual stomach	0	2	
Mean tumor size	17.5	15.6	NS
Histological type			
Well differentiated	58	149	NS
Moderately differentiated	5	10	NS
Poorly differentiated	0	8	NS
Papillary differentiated	1	1	NS
Category of indication			
Guideline lesion	47	118	NS
Lesion included in the expanded indications	17	50	NS

NS: Not significant.

significantly different to that of the non-older group.

Tumor characteristics

No significant between-group differences were found regarding the macroscopic type, tumor size, histological type, and ESD indication categories (Table 2). However, the proportion of upper lesions was significantly higher in the older group (43.8%) than in the non-older group (23.2%) (P = 0.0042).

Technical outcomes

The R0 resection rate in the non-older group was significantly higher than that in the older group (100% *vs* 95.3%, P = 0.02, Table 3). However, the R0 resection rate was greater than 95% in both groups. The postoperative bleeding rates of the older and non-older groups were 1.6% (1/64) and 4.8% (8/168), respectively. Perforation occurred in only one (1.6%) patient in the older group; endoscopic clipping was performed in this patient and the

Table 3 Technical outcome *n* (%)

	Older group (*n* = 64)	Non-older group (*n* = 168)	*P* value
En bloc resection	63 (98.4)	168 (100)	NS
R0 resection	61 (95.3)	168 (100)	0.03
Complications			
Intraoperative hemorrhage	0 (0)	0 (0)	NS
Intraoperative perforation	1 (1.6)	0 (0)	NS
Postoperative hemorrhage	1 (1.6)	8 (4.8)	NS
Postoperative perforation	0 (0)	0 (0)	NS

NS: Not significant.

Table 4 Social and economic outcomes *n* (%)

Parameter	Older group (*n* = 64)	Non-older group (*n* = 168)	*P* value
Worsening of the performance status	3/64 (4.7)	1/168 (0.6)	NS
Mean duration of hospitalization (d)	11.4	10.7	NS
Mean financial cost of admission (JPY)	657040	574890	NS

NS: Not significant.

perforation was cured. There was no significant difference between the two groups in the rate of ESDCC-related complications.

Social and economic outcomes

Three patients in the older group and one patient in the non-older group showed a worse PS after ESD, but there was no significant difference between groups in the prevalence of a worse PS after ESD. The mean duration of hospitalization in the older and non-older groups was 11.4 and 10.7 d, respectively. The mean financial costs of admission for the older and non-older groups were 657040 JPY and 574890 JPY, respectively. There were no significant differences between the two groups in duration of hospitalization or admission costs (Table 4).

DISCUSSION

According to the 2014 fiscal statistics published by the Ministry of Health, Labour and Welfare, the life expectancies of men and women are 80.5 years old and 86.8 years old, respectively[20]. The natural history of EGC is unclear. However, a long life expectancy and an aging population will inevitably lead to an increased number of older patients with EGC in Japan. Long-term outcomes suggest that implementation of ESD for older patients with a satisfactory PS will increase life expectancy[21]. Therefore, we investigated the clinical outcomes associated with older patients who received ESDCC for EGC, including economic and social aspects.

As expected, older patients in our study had significantly more pre-existing comorbidities than did non-older patients. In our study, the rate of pre-existing comorbidities was higher than that in previous reports because the mean age of our patients was older than that in previous reports[8,22]. Tokioka *et al*[8] and Chinda *et al*[22] reported that older patients were more likely to receive anticoagulant therapy than non-older patients. However, the proportions of older and non-older patients in our study who received anticoagulant therapy were almost equal. The current study included five (7.8%) and four (2.4%) patients who had PSs of 3 and 4 in the older group and the non-older group, respectively, as they strongly desired treatment. The PSs of these patients did not change after the procedure. However, three (4.7%) patients in the older group and one (0.6%) patient with senile dementia in the non-older group showed a worse PS after ESD. Three patients in the older group had several pre-existing comorbidities. Although ESD is less invasive than an operation, care should be taken regarding patients with several pre-existing comorbidities.

No significant between-group differences were observed regarding macroscopic type, tumor size, histological type, and ESD indication categories. ESD was performed on the lesions of these patients, similar to a previous report[8]. In our study, the proportion of upper lesions was significantly higher in the older group than in the non-older group. Furthermore, the R0 resection rate in the non-older group was significantly higher than that in the older group. The tumor location likely affects the difficulty of the ESD procedure, and so the greater number of upper lesions in older patients might have affected the technical outcomes.

The current study did not show a significant difference between older and non-older patients in the rate of ESDCC-related complications (*i.e.*, postoperative bleeding and perforation). The reported perforation and bleeding rates of ESD using a knife device range from 1.2% to 8.2% and from 5.3% to 15.6%, respectively[23-30]. Our complication rate was low compared with that reported in previous studies that used conventional knives[23-30]. Inevitable risk factors associated with knife devices for ESD-related complications include defects of fixation (inaccurate targeting) and compression (hemostatic effect), as well as pushing the knife into the target tissue (where the pushing force is in the direction of the muscle layer) with an electric discharge[14]. The CC can accurately grasp target tissue and can be energized or incised while separated from the muscular layer, thus greatly reducing the risks. There was no uncontrollable intraoperative bleeding in our previous reports on ESD[11-17]. We were able to quickly and easily stop intraoperative bleeding using the CC[15] without changing the device for the entire gastrointestinal tract. In the present study, we did not perform any unexpected incisions. Therefore, the CC has the potential to decrease the risk of ESD-related complications in older and non-older patients.

Our study found no significant difference between older and non-older patients in the mean duration of hospitalization. Tokioka *et al*[8] also failed to find a significant difference in the mean duration of hospitalization between these two groups (13.3 d *vs* 10.3 d). However, these authors reported that older patients with complications due to ESD (*i.e.*, perforation) were hospitalized for significantly longer periods than non-older patients[8]. In our series, we encountered perforation in one older patient who underwent endoscopic clipping and required 16 d of hospitalization. Therefore, preventing complications, such as perforation, is important for reducing the duration of hospitalization, especially in older patients.

Few medical economic outcomes have been reported in older patients. Murata *et al*[31] reported that mean medical costs are significantly higher for older patients undergoing ESD for EGC than for non-older patients. They also reported that chronic comorbid conditions or the use of anticoagulant drugs, as well as the occurrence of complications, might be associated with an increase in the length of stay or medical costs during hospitalization[31]. Although the older group in our study showed a significantly higher rate of comorbid cardiovascular disease than did the non-older group, the postoperative bleeding rate was low in the older group (1.6%). In our series, there were no significant between-group differences in the length of stay and medical costs during hospitalization. The reported complication rate associated with ESDCC is lower than that of ESD using conventional knives[11-17], which might have affected our medical economic outcomes.

We conclude that ESDCC is safe and effective for older and non-older patients with EGC. This study is limited by its retrospective nature. A prospective study with a larger sample size is advised.

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COMMENTS

Background

In an aging society, the opportunity to treat older patients with early gastric cancer (EGC) is increasing. However, there is little information on the medical costs of endoscopic submucosal dissection (ESD), the mean duration of hospitalization, and the change in performance status before and after ESD. It is important to assess the clinical outcomes of ESD using the Clutch Cutter (CC) (ESDCC) in older patients with EGC.

Research frontiers

The authors previously showed that ESD using the CC (ESDCC) is a safe and effective method for treating patients with early cancer in the gastrointestinal tract. No reports have yet evaluated the efficacy and safety of ESDCC for older patients with EGC, including the economic and social aspects.

Innovations and breakthroughs

There was no significant difference between older patients and non-older patients in mean duration of hospitalization, incidence of ESDCC-related complications, change in PS before and after ESD, and financial cost of admission.

Application

It may be economically and socially beneficial to reduce the complication rate by performing ESDCC for older patients with EGC.

Terminology

The CC (DP2618DT, Fujifilm Corporation, Tokyo, Japan) was developed by Akahoshi. The CC is a grasping type of scissors/forceps that can grasp tissue pieces and cut or coagulate with an electrosurgical current. To facilitate tissue grasping, the CC has a serrated cutting edge with a width of 0.4 mm, and a length of 3.5 mm or 5 mm. The forceps diameter is 2.7 mm. The outside of the forceps is insulated so that electrosurgical current energy concentrates on the closure blade to avoid unintentional incision. Furthermore, the forceps can be rotated in any desired direction. The CC is disposable and cannot be reused. The CC can be used in all steps of ESD.

Peer-review

The authors present an interesting study on the efficacy and safety of endoscopic submucosal dissection for older patients with early gastric cancer. The study is well designed, the results are accurately noted and the discussion is concise.

REFERENCES

1 **Arai T**, Esaki Y, Inoshita N, Sawabe M, Kasahara I, Kuroiwa K, Honma N, Takubo K. Pathologic characteristics of gastric cancer in the elderly: a retrospective study of 994 surgical patients. *Gastric Cancer* 2004; **7**: 154-159 [PMID: 15449203 DOI: 10.1007/s10120-004-0285-4]

2 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]

3 **Abe N**, Yamaguchi Y, Takeuchi H, Izumisato Y, Yanagida O, Masaki T, Mori T, Sugiyama M, Atomi Y. Key factors for successful en bloc endoscopic submucosal dissection of early stage gastric cancer using an insulation-tipped diathermic knife. *Hepatogastroenterology* 2006; **53**: 639-642 [PMID: 16995479]

4 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627 DOI: 10.1007/s10120-006-0389-0]

5 **Gotoda T**. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1-11 [PMID: 17334711 DOI: 10.1007/s10120-006-0408-1]

6 **Kakushima N**, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Yahagi N, Omata M. Technical feasibility of endoscopic submucosal dissection for gastric neoplasms in the elderly Japanese population. *J Gastroenterol Hepatol* 2007; **22**: 311-314 [PMID: 17295759 DOI: 10.1111/j.1440-1746.2006.04563.x]

7 **Kim BJ**, Chang TH, Kim JJ, Min BH, Lee JH, Son HJ, Rhee PL, Rhee JC, Kim KM, Park CK. Efficacy and safety of endoscopic submucosal dissection for early gastric cancer in patients with comorbid diseases. *Gut Liver* 2010; **4**: 186-191 [PMID: 20559520 DOI: 10.5009/gnl.2010.4.2.186]

8 **Tokioka S**, Umegaki E, Murano M, Takeuchi N, Takeuchi T, Kawakami K, Yoda Y, Kojima Y, Higuchi K. Utility and problems of endoscopic submucosal dissection for early gastric cancer in elderly patients. *J Gastroenterol Hepatol* 2012; **27** Suppl 3: 63-69 [PMID: 22486874 DOI: 10.1111/j.1440-1746.2012.07075.x]

9 **Onozato Y**, Ishihara H, Iizuka H, Sohara N, Kakizaki S, Okamura S, Mori M. Endoscopic submucosal dissection for early gastric cancers

and large flat adenomas. *Endoscopy* 2006; **38**: 980-986 [PMID: 17058161 DOI: 10.1111/j.1443-1661.2007.00763.x]

10 **Abe N**, Gotoda T, Hirasawa T, Hoteya S, Ishido K, Ida Y, Imaeda H, Ishii E, Kokawa A, Kusano C, Maehata T, Ono S, Takeuchi H, Sugiyama M, Takahashi S. Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older. *Gastric Cancer* 2012; **15**: 70-75 [PMID: 21667133 DOI: 10.1007/s10120-011-0067-8]

11 **Akahoshi K**, Akahane H, Murata A, Akiba H, Oya M. Endoscopic submucosal dissection using a novel grasping type scissors forceps. *Endoscopy* 2007; **39**: 1103-1105 [PMID: 18072064 DOI: 10.1055/s-2007-966842]

12 **Akahoshi K**, Honda K, Akahane H, Akiba H, Matsui N, Motomura Y, Kubokawa M, Endo S, Higuchi N, Oya M. Endoscopic submucosal dissection by using a grasping-type scissors forceps: a preliminary clinical study (with video). *Gastrointest Endosc* 2008; **67**: 1128-1133 [PMID: 18355820 DOI: 10.1016/j.gie.2007.12.007]

13 **Akahoshi K**, Akahane H, Motomura Y, Kubokawa M, Itaba S, Komori K, Nakama N, Oya M, Nakamura K. A new approach: endoscopic submucosal dissection using the Clutch Cutter® for early stage digestive tract tumors. *Digestion* 2012; **85**: 80-84 [PMID: 22269283 DOI: 10.1159/000334647]

14 **Akahoshi K**, Akahane H. A new breakthrough: ESD using a newly developed grasping type scissor forceps for early gastrointestinal tract neoplasms. *World J Gastrointest Endosc* 2010; **2**: 90-96 [PMID: 21160708 DOI: 10.4253/wjge.v2.i3.90]

15 **Akahoshi K**, Motomura Y, Kubokawa M, Gibo J, Kinoshita N, Osada S, Tokumaru K, Hosokawa T, Tomoeda N, Otsuka Y, Matsuo M, Oya M, Koga H, Nakamura K. Endoscopic Submucosal Dissection for Early Gastric Cancer using the Clutch Cutter: a large single-center experience. *Endosc Int Open* 2015; **3**: E432-E438 [PMID: 26528497 DOI: 10.1055/s-0034-1392509]

16 **Akahoshi K**, Minoda Y, Komori K, Motomura Y, Kubokawa M, Otsuka Y, Hamada S, Fukuda S, Iwao R, Gibo J, Oya M, Nakamura K. Endoscopic submucosal dissection using the "Clutch Cutter" for early esophageal squamous cell carcinoma. *Endoscopy* 2013; **45**: 1035-1038 [PMID: 24163190 DOI: 10.1055/s-0033-1344863]

17 **Minoda Y**, Akahoshi K, Otsuka Y, Kubokawa M, Motomura Y, Oya M, Nakamura K. Endoscopic submucosal dissection of early duodenal tumor using the Clutch Cutter: a preliminary clinical study. *Endoscopy* 2015; **47** Suppl 1 UCTN: E267-E268 [PMID: 26099085 DOI: 10.1055/s-0034-1392209]

18 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739 DOI: 10.1007/PL00011720]

19 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123 [PMID: 21573742 DOI: 10.1007/s10120-011-0042-4]

20 **Statistics and Information Department**, Minister's Secretariat, Ministry of Health and welfare of Japan. The abridged life table. Tokyo, 2014. Available from: URL: http://www.mhlw.go.jp/english/database/db-hw/lifetb14/

21 **Kusano C**, Iwasaki M, Kaltenbach T, Conlin A, Oda I, Gotoda T. Should elderly patients undergo additional surgery after non-curative endoscopic resection for early gastric cancer? Long-term comparative outcomes. *Am J Gastroenterol* 2011; **106**: 1064-1069 [PMID: 21407189 DOI: 10.1038/ajg.2011.49]

22 **Chinda D**, Sasaki Y, Tatsuta T, Tsushima K, Wada T, Shimoyama T, Fukuda S. Perioperative complications of endoscopic submucosal dissection for early gastric cancer in elderly Japanese patients 75 years of age or older. *Intern Med* 2015; **54**: 267-272 [PMID: 25748734 DOI: 10.2169/internalmedicine.54.3300]

23 **Chung IK**, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009; **69**: 1228-1235 [PMID: 19249769 DOI: 10.1016/j.gie.2008.09.027]

24 **Mannen K**, Tsunada S, Hara M, Yamaguchi K, Sakata Y, Fujise T, Noda T, Shimoda R, Sakata H, Ogata S, Iwakiri R, Fujimoto K. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. *J Gastroenterol* 2010; **45**: 30-36 [PMID: 19760133 DOI: 10.1007/s00535-009-0137-4]

25 **Watari J**, Tomita T, Toyoshima F, Sakurai J, Kondo T, Asano H, Yamasaki T, Okugawa T, Ikehara H, Oshima T, Fukui H, Miwa H. Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study. *World J Gastrointest Endosc* 2013; **5**: 281-287 [PMID: 23772265 DOI: 10.4253/wjge.v5.i6.281]

26 **Nonaka K**, Kita H. Endoscopic submucosal dissection for early gastric cancer. *J Cancer Ther* 2013; **4**: 26-32 [DOI: 10.4236/jct.2013.41A004]

27 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973 [PMID: 17524403 DOI: 10.1111/j.1443-1661.2005.00459.x]

28 **Tsuji Y**, Ohata K, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J Gastroenterol* 2010; **16**: 2913-2917 [PMID: 20556838 DOI: 10.3748/wjg.v16.i23.2913]

29 **Fujishiro M**, Chiu PW, Wang HP. Role of antisecretory agents for gastric endoscopic submucosal dissection. *Dig Endosc* 2013; **25** Suppl 1: 86-93 [PMID: 23368844 DOI: 10.1111/j.1443-1661.2012.01370.x]

30 **Koh R**, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, Numata K, Kokawa A, Sasaki T, Nozawa A, Taguri M, Morita S, Maeda S, Tanaka K. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. *Gastrointest Endosc* 2013; **78**: 476-483 [PMID: 23622974 DOI: 10.1016/j.gie.2013.03.008]

31 **Murata A**, Muramatsu K, Ichimiya Y, Kubo T, Fujino Y, Matsuda S. Endoscopic submucosal dissection for gastric cancer in elderly Japanese patients: an observational study of financial costs of treatment based on a national administrative database. *J Dig Dis* 2014; **15**: 62-70 [PMID: 24127880 DOI: 10.1111/1751-2980.12106]

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EVIDENCE-BASED MEDICINE

Low-dose computed tomography with 4th-generation iterative reconstruction algorithm in assessment of oncologic patients

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Abstract

AIM

To compare radiation dose and image quality of low-dose computed tomography (CT) protocol combined with hybrid-iterative reconstruction algorithm with standard-dose CT examinations for follow-up of oncologic patients.

METHODS

Fifty-one patients with known malignant diseases which underwent, during clinical follow-up, both standard-dose and low-dose whole-body CT scans were enrolled. Low-dose CT was performed on 256-row scanner, with 120 kV and automated mA modulation, and iterative reconstruction algorithm. Standard-dose CT was performed on 16-rows scanner, with 120 kV, 200-400 mAs (depending on patient weight). We evaluated density values and signal-to-noise ratio, along with image noise (SD), sharpness and diagnostic quality with 4-point scale.

RESULTS

Density values in liver, spleen and aorta were higher in low-dose images (liver 112.55 HU *vs* 103.90 HU, $P < 0.001$), as SD values in liver and spleen (liver 16.81 *vs* 14.41). Volumetric-Computed-Tomographic-Dose-Index (CTDIvol) and Dose-Length-Product (DLP) were significantly lower in low-dose CT as compared to standard-dose (DLP 1025.6 mGy*cm *vs* 1429.2 mGy*cm, $P < 0.001$) with overall dose reduction of 28.9%. Qualitative analysis did not reveal significant differences in image noise and diagnostic quality.

CONCLUSION

Automatic tube-current modulation combined with hybrid-iterative algorithm allows radiation dose reduction of 28.9% without loss of diagnostic quality, being useful in reducing dose exposure in oncologic patients.

Key words: Computed tomography; Low-dose computed tomography; Tube current modulation; Oncologic imaging; Radiation dose

Core tip: Introduction of new generation of multidetector computed tomography (MDCT) scanner allowed thin-collimation scanning and high spatial resolution, and reducing at same time the delivered radiation dose to patients by using new iterative reconstruction algorithm. This new mathematical model approach permits to reduce the radiation dose, expecially in patients who undergo serial follow-up study for oncologic (staging and restaging) purpose. On these basis in our study we evaluated radiation dose and image quality of CT examinations in a population of oncologic patients undergoing follow-up examinations with a new generation MDCT scanner (256-rows) using automatic modulation of tube current and iterative reconstruction algorithm (DoseRight system).

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INTRODUCTION

Since the advent of computed tomography (CT) and, more recently, the development of multidetector computed tomography (MDCT) technique, the number of CT scans have increased significantly[1,2]; according to National Council on Radiation Protection and Measurements (NCRP) report 160, in 2006 United States population was exposed to more than seven times ionizing radiation from medical procedures than in the early 1980's, and CT contributes to nearly one-half of all this radiation imaging exposure[1,2]. This high number of CT examinations have raised concern because of the potential risk of radiation-induced malignancy[3].

In the clinical management of patients with malignant diseases CT, with other cross-sectional imaging techniques such as MRI and FDG-PET/CT, has a major role for initial diagnosis of the disease, for staging, and during follow-up to monitor response to treatment and evaluate disease remission or relapse[4]. CT of the chest, abdomen and pelvis has the ability to obtain a global evaluation of the patient and to depict both primary tumor and metastasis in most cases, more quickly, safely and accurately than other more invasive or less sensitive imaging techniques. On these bases, oncologic patients typically undergo multiple CT investigations during their clinical follow-up, and risks derived from repeated scans and exposure to ionizing radiation should be balanced against the benefits of diagnostic imaging: CT examinations must have a correct clinical justification, and every CT scans must be technically optimized to keep radiation doses as low as possible while providing requested diagnostic information[5,6].

To optimize radiation dose in CT various technological strategies can be applied: These include active management of individual acquisition parameters (number of phases, section thickness, peak voltage, tube current-time product, pitch) or using an automated exposure control system[7]. Recently, iterative reconstruction algorithms have been introduced to reduce image noise, allowing further reduction in radiation dose beyond levels previously achievable with filtered back projection reconstruction (FBP)[7]. iDose^4 is a hybrid iterative algorithm that is able to reduce noise on both the raw and image data[8,9]. The purpose of our study was to evaluate the radiation dose and image quality of CT examinations in a population of oncologic patients undergoing follow-up examinations comparing a new generation MDCT scanner (256-rows), using automatic modulation of tube current and iterative reconstruction algorithm (DoseRight system and iDose^4), with a 16-MDCT scanner using standard dose protocol and FBP.

MATERIALS AND METHODS

Patients population

Institutional research board approval was obtained for this retrospective study with waiver of the requirement for written consent.

Between August 2013 and April 2015, 259 adult patients (> 18 years old) with known malignant diseases (32 lung, 9 colorectal, 3 ovarian, 3 stomach, 2 uterine, 1 non hodgkin lymphoma and 1 testicular) underwent contrast enhanced chest-abdomen-pelvis CT examination in a single venous phase during their clinical follow-up on a 256-MDCT scanner with a protocol implemented in our institution from August 2013 (with automatic modulation of current tube and iDose^4 reconstruction algorithm). These examinations were identified with a retrospective

Table 1 Descriptive table of weight groups in the patients population (n = 51)

Weight groups	No. of patients	M/F	Mean ± SD (yr)
Group A (41-60 kg)	8	3/5	70.5 ± 8.6
Group B (61-80 kg)	25	9/16	67.6 ± 11.5
Group C (81-90 kg)	13	11/2	71.8 ± 7.4
Group D (> 90 kg)	5	4/1	59.2 ± 10.1
All patients	51	34/18	68.3 ± 10.4

M: Male; F: Female.

review of CT studies archived with PACS system (AGFA Diagnostic Software, Impax, version 6.4.0.3125; Agfa, Mortsel; Belgium). In this group we selected patients which had undergone also standard-dose contrast enhanced CT scan on a 16-MDCT in a different time. Fifty-one patients were finally selected as our study group and were categorized into four groups according to their weight (kg): 41-60 kg (group A), 61-80 kg (group B), 81-90 kg (group C) and > 90 kg (group D) (Table 1). Total mean weight was not statistically different between the two scans (74.1 ± 14.9 kg for lower dose scans and 73.9 ± 15.0 kg for standard dose scans, P = 0.705). The mean time interval between CT acquisitions was 4.8 ± 2.9 mo. Patients' mean age, calculated at the time of the most recent CT scan, was 68.3 ± 10.4 years old.

MDCT technique and image reconstruction

All 51 patients had undergone thorax-abdomen-pelvis CT examinations both on a 16-rows MDCT scanner (Brilliance, Philips Medical Systems, Eindhoven, The Netherlands) and on a 256-rows MDCT (iCT, Philips).

For both examinations, CT data were acquired after the intravenous bolus injection of non-ionic iodinated contrast material (Xenetix 350; Guerbet, Aulnay, France), injected using a 18-gauge catheter positioned into the antecubital vein at a rate of 3.5 mL/s, with image acquisition during portal venous phase (55-70 s after the initiation of the contrast bolus), in accordance with an institutionally defined protocol. The volume of contrast agent was calculated on the basis of the patient's body weight, with total dose ranging from 80 to 130 mL, and it was followed by a saline flush of 50 mL of NaCl at 3.5 mL/s. The patients were instructed to hold their breath during scanning. All studies were started from the lung apices and proceeded in a cephalocaudal direction until ischial tuberosity, to include chest, abdomen and pelvis of the patients.

The technical parameters for scanning included: (1) for 16-rows CT scanner: 120 kVp, mAs depending on patients' weight (41-60 kg: 200 mAs; 61-80 kg: 300 mAs; 81-90 kg: 350 mAs; > 90 kg: 400 mAs), section thickness 2 mm, pitch 0.813, 0.75 s rotation time, display field of view (FOV) depending on the patient's physique (median values of 350), beam collimation 16 × 1.5; (2) for 256-rows CT scanner: 120 kVp, automated mAs with X-ray tube current automatic modulation system (range of mean mAs: 103-468 mAs), section thickness 2 mm, pitch 0.984, 0.75 s rotation time, display field of view (FOV) depending on the patient's physique (median values of 350), beam collimation 64 mm × 0.625 mm (to reduce the overranging and to improve the Z-DOM modulation performance). The Brilliance iCT scanner can control radiation exposure with advanced dose reduction tools, such as X-ray tube current automatic modulation system (the automatic current selection ACS, which automatically suggests tube current settings according to estimated patient diameter in the scan region, and the Z-axis dose modulation system Z-DOM, that modulates mA along the patient longitudinal axis using the attenuation profile estimated from the Surview), SmartShape and IntelliBeam shaping filters, the Eclipse asymmetric collimator for over-ranging reduction, NanoPanel^{3D} detectors and ClearRay 2D anti-scatter grid[10].

The 16-MDCT images were reconstructed using a standard FBP algorithm with a standard soft-tissue kernel, while the 256-MDCT images were reconstructed with hybrid iterative reconstruction algorithm (iDose^4): iDose^{4}Level 3 was chosen[8].

At the end of every examinations, the volumetric computed tomographic dose index (CTDIvol) and the dose-length product (DLP) were provided by the scanners in the dosimetric report.

CT values (HU) and standard deviation of CT values (SD) were also measured by placing one ROI (2 cm^2) within the subcutaneous fat of the anterior abdominal wall. SNR was calculated for the liver and the spleen as: $SNR = HU_{ROI}/SD_{ROI}$, where HU_{ROI} is the mean CT value in Hounsfield units of the tissue and SD_{ROI} the standard deviation of CT values in the same ROI.

Statistical analysis

Continuous variables (HU, SD, SNR, DLP, CTDIvol, patients weight) were presented as means ± SD. The Wilcoxon signed-rank test for paired samples or paired Student t-test were used, where appropriate, to compare values of continuous variables between standard dose protocol images and lower dose protocol images. To evaluate differences in qualitative analysis between the two protocols the Wilcoxon signed-rank test for paired samples was applied. A P-value < 0.05 was considered statistically significant.

Cohen's kappa was used to evaluate agreement between the two readers[11]. Analysis was performed with commercially available statistical software (SPSS Statistics 17.0, Chicago, IL).

RESULTS

Radiation dose

Mean values of obtained DLP and CTDIvol were significantly lower with low-dose protocol in comparison with standard dose protocol (P < 0.001): For lower-dose CT, DLP and CTDIvol were respectively 1025.6 ±

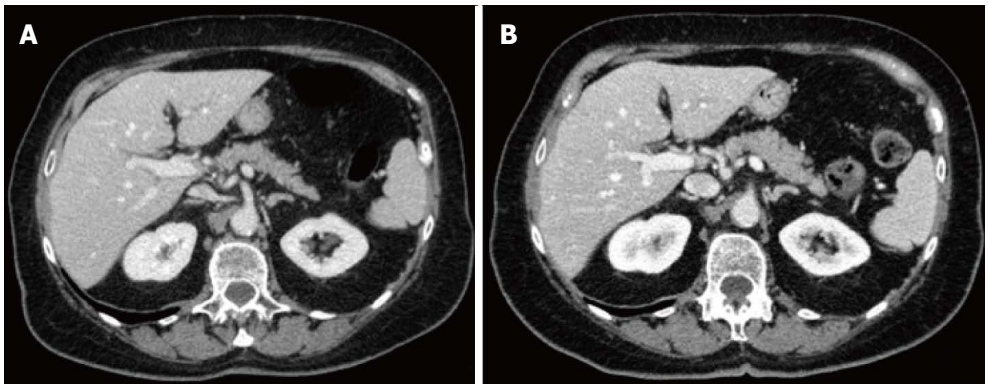

Figure 1 Axial contrast-enhanced computed tomography images at the level of upper abdomen obtained in a 81 years old female patient with lung cancer (height 160 cm, weight 61 kg). A: Standard dose protocol (120 kV, 300 mAs, DLP 1317.4 mGy*cm, CDTI 21.1 mGy); B: Lower dose protocol (120 kV, 142-222 mAs, DLP 846.0 mGy*cm, CDTI 13.6 mGy): Lower dose image shows increased sharpness and enhancement in comparison with standard dose image in spite of mild increase of noise, and similar diagnostic quality with a 35.8% Dose-Length-Product reduction.

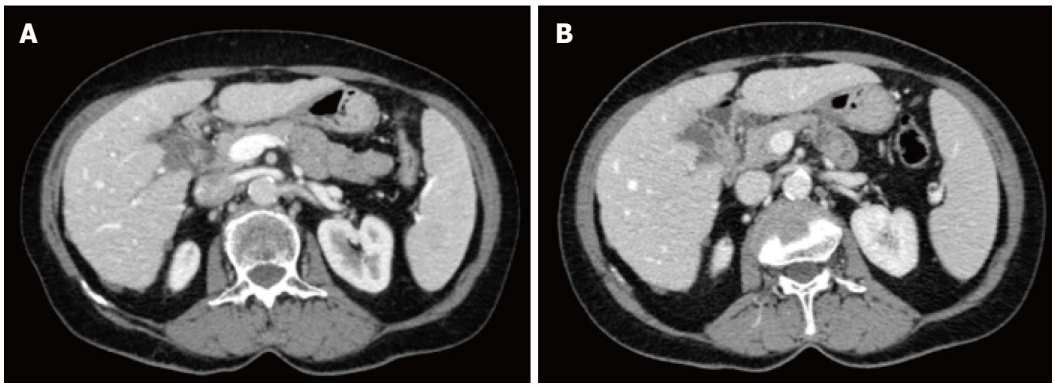

Figure 2 Axial contrast-enhanced computed tomography images at the level of upper abdomen obtained in a 70 years old female patient with ovarian cancer and some small hypoattenuating hepatic subcapsular implants with well-defined margins (height 160 cm, weight 68 kg). A: Standard dose protocol (120 kV, 300 mAs, Dose-Length-Product 1304.6 mGy*cm, CDTI 21.0 mGy); B: Lower dose protocol (120 kV, 123-231 mAs, Dose-Length-Product 840.9 mGy*cm, CDTI 13.1 mGy).

370.9 mGy*cm and 15.4 ± 5.2 mGy, compared with 1429.2 ± 297.7 mGy*cm and 21.4 ± 4.0 mGy for standard-dose protocol. The low-dose protocol provided a mean DLP reduction of 28.9% compared to standard-dose protocol (Figure 1).

The average weight was 74.1 ± 14.9 kg for low dose scans (range 41-114 kg) and 73.9 ± 15.0 kg for standard dose scans (range 43-114 kg) (P = 0.705). By dividing patients into four groups of weight, we obtained a higher rate of DLP reduction in patients in groups A, B and C with a statistically significant difference between the two protocols; in patients with high weight (> 90 kg, group D), for values of DLP and CTDIvol only few differences between the two protocols were recorded, not statistically significant, with a radiation dose reduction of 2.5% (Table 2).

Qualitative analysis

Qualitative analysis results are shown in Table 3. There was a good inter-reader agreement, as shown by k Cohen values. There weren't significant differences in the qualitative evaluation of image noise and diagnostic quality for both readers (Figure 2), and of image sharpness for one reader. The other reader assigned to low-dose images superior grades for sharpness, with a significant difference (P = 0.012).

Quantitative analysis

CT values of density (HU) measured within abdominal aortic lumen and liver and spleen parenchyma were significantly higher using low-dose CT with iDose[4] (P < 0.001) (Table 4). The mean liver and spleen parenchymal noise (SD) was higher with low-dose protocol as well, while SD of abdominal subcutaneous fat was higher but without reaching statistical significance. The measured noise varied according to the weight of the patients, with higher values of SD in patients with higher weight; values of SD in the liver parenchyma with low-dose protocol vs standard protocol were respectively 14.62 ± 1.80 *vs* 11.62 ± 2.03 in group A, 16.66 ± 1.45 *vs* 13.10 ± 2.18 in group B, 18.03 ± 1.98 *vs* 16.26 ± 1.54 in group C and 17.91 ± 2.24 *vs* 20.59 ± 3.28 in group D.

SNR values, calculated as SNR = HU_{ROI}/SD_{ROI}, were lower in low-dose images, reaching a significant difference within the liver parenchyma (6.94 ± 1.32 *vs* 7.80 ± 2.30, P = 0.002) and without statistical

Table 2 Comparison of Dose-Length Product and Volumetric Computed Tomographic Dose Index obtained with standard-dose and low-dose protocols in all patients (n = 51) and according to weight (kg)

BMI groups	No. of patients	CTDIvol (mGy)			DLP (mGy*cm)			% DLP reduction
		Standard-dose	Low-dose	*P*-value	Standard-dose	Low-dose	*P*-value	
Group A (41-60 kg)	8	14.1 ± 0.0	9.8 ± 1.5	0.012	891.9 ± 36.3	627.5 ± 92.9	0.012	29.6
Group B (61-80 kg)	25	21.1 ± 0.0	14.0 ± 2.8	< 0.001	1386.6 ± 65.9	920.0 ± 175.0	< 0.001	33.5
Group C (81-90 kg)	13	24.6 ± 0.0	17.2 ± 2.9	0.001	1656.8 ± 61.2	1162.6 ± 204.2	0.001	29.9
Group D (> 90 kg)	5	27.4 ± 1.5	26.5 ± 5.4	0.5	1910.4 ± 147.6	1835.1 ± 359.5	0.5	2.5
All patients	51	21.4 ± 4.0	15.4 ± 5.2	< 0.001	1429.2 ± 297.7	1025.6 ± 370.9	< 0.001	28.9

DLP: Dose-Length-Product; CTDIvol: Volumetric Computed Tomographic Dose Index.

Table 3 Qualitative scoring of image noise, image sharpness and diagnostic quality of computed tomography images from Reader 1 and Reader 2

	Image noise		Image sharpness		Diagnostic quality	
	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2
Low-dosea	3.4 ± 0.6	3.6 ± 0.6	3.7 ± 0.5	3.7 ± 0.5	3.7 ± 0.5	3.8 ± 0.4
Group A (n = 8)	3.6 ± 0.7	3.8 ± 0.5	3.6 ± 0.5	3.5 ± 0.5	3.9 ± 0.4	3.8 ± 0.5
Group B (n = 25)	3.4 ± 0.6	3.6 ± 0.6	3.8 ± 0.5	3.8 ± 0.4	3.7 ± 0.6	3.8 ± 0.4
Group C (n = 13)	3.1 ± 0.4	3.6 ± 0.5	3.6 ± 0.5	3.9 ± 0.4	3.6 ± 0.5	4.0 ± 0.0
Group D (n = 5)	3.3 ± 0.6	3.0 ± 1.0	4.0 ± 0.0	3.3 ± 0.6	4.0 ± 0.0	3.7 ± 0.6
Standard-doseb	3.6 ± 0.7	3.5 ± 0.6	3.3 ± 0.7	3.5 ± 0.6	3.7 ± 0.5	3.8 ± 0.4
Group A (n = 8)	3.9 ± 0.4	3.5 ± 0.5	3.1 ± 0.6	3.4 ± 0.5	3.9 ± 0.4	3.8 ± 0.5
Group B (n = 25)	3.7 ± 0.5	3.7 ± 0.5	3.5 ± 0.6	3.5 ± 0.6	3.8 ± 0.4	3.8 ± 0.4
Group C (n = 13)	3.3 ± 0.5	3.3 ± 0.5	2.9 ± 0.7	3.9 ± 0.4	3.6 ± 0.5	4.0 ± 0.0
Group D (n = 5)	2.3 ± 1.5	3.0 ± 1.0	3.0 ± 1.0	3.3 ± 0.6	2.7 ± 1.2	3.7 ± 0.6
P-valuea-b	0.292	0.655	0.012	0.088	0.437	0.206
k Cohen Reader 1-Reader 2	0.694a-0.756b		0.783a-0.672b		0.704a-0.786b	

Table 4 Computed tomography values (HU), standard deviation of computed tomography values (SD) and signal-to-noise ratio obtained with standard-dose and low-dose protocols

	Low-dose	Standard-dose	*P*-value
HU_{aorta} (n = 51)	166.20 ± 18.83	154.17 ± 24.82	< 0.001
HU_{liver} (n = 51)	112.55 ± 16.49	103.90 ± 17.49	< 0.001
HU_{spleen} (n = 51)	126.24 ± 13.60	112.77 ± 15.66	< 0.001
SD_{liver} (n = 51)	16.81 ± 2.02	14.41 ± 3.33	< 0.001
SD_{spleen} (n = 51)	16.78 ± 2.04	14.72 ± 3.26	< 0.001
SD_{fat} (n = 51)	12.17 ± 2.77	12.07 ± 2.98	0.307
SNR_{liver} (n = 51)	6.94 ± 1.32	7.80 ± 2.30	0.002
SNR_{liver} Group A (n = 8)	8.09 ± 1.63	9.36 ± 2.27	0.05
SNR_{liver} Group B (n = 25)	6.95 ± 1.22	8.53 ± 1.97	< 0.001
SNR_{liver} Group C (n = 13)	6.47 ± 1.00	6.66 ± 1.34	0.972
SNR_{liver} Group D (n = 5)	6.29 ± 1.19	4.60 ± 1.77	0.08
SNR_{spleen} (n = 51)	7.73 ± 1.46	8.10 ± 2.04	0.153
SNR_{spleen} Group A (n = 8)	9.25 ± 2.31	10.53 ± 1.69	0.092
SNR_{spleen} Group B (n = 25)	7.60 ± 1.10	8.04 ± 1.86	0.177
SNR_{spleen} Group C (n = 13)	7.26 ± 1.11	7.20 ± 1.45	0.65
SNR_{spleen} Group D (n = 5)	7.21 ± 0.82	6.86 ± 1.89	0.893

SNR: Signal-to-noise ratio.

significance within spleen parenchyma (7.73 ± 1.46 *vs* 8.10 ± 2.04, P = 0.153). When SNR data were reviewed according to the weight of patients, SNR values decreased as patients' weight increased. SNR values were lower in low-dose protocol in comparison with standard-dose protocol in groups A and B, comparable between two protocols in group C and higher in group D (Table 3).

DISCUSSION

In the latest years many studies investigating the potential of radiation dose reduction by applying different iterative reconstruction algorithms have been published for abdomen, chest, head, coronary and chest angiography, and they showed significant dose reduction while maintaining, or sometimes improving, image quality[12-26].

Arapakis *et al*[12] addressed the effect of iterative algorithm on radiation dose and image quality of chest-abdomen-pelvis (CAP) CT scans. They applied iDose^4 hybrid iterative reconstruction algorithm in a group of 84 patients and compared images to those obtained with "old standard" protocol with filtered back projection reconstruction algorithm in a group of 99 patients, obtaining an overall 46.5% decrease in effective dose with lower image noise and higher values of SNR and CNR; in their study, the greatest dose reduction was recorded in patients with lower weight[12].

Karpitschka *et al*[13] retrospectively evaluated 40 patients which underwent CT scans for staging of malignancy with both a standard-dose (tube current time product 250 mAs and FBP reconstruction) and a reduced-dose CT scan (150 mAs and with Iterative Reconstruction

in Image Space IRIS), obtaining a greater than 45% dose reduction at maintained image quality; the authors recommend the use of IR in oncological patients in order to reduce radiation dose to patients.

Moreover, for abdominal CT scans, Prakash *et al*[14] showed a reduction of radiation dose by 25% using weight-based adjustment of automatic exposure control technique and Adaptive Statistical Iterative Reconstruction (ASIR) in comparison with FBP reconstructed scans, while May *et al*[15] obtained a 50% reduction in abdominal CT by using IRIS.

In our study, values of DLP obtained using a low-dose protocol with iDose^4 iterative algorithm were, on average, 28.9% lower compared to our standard dose with FBP reconstruction. Despite higher levels of quantitative noise (as demonstrated by SD values) within liver and spleen parenchyma, however, qualitative analysis didn't reveal significant differences in overall image noise and diagnostic quality when compared with standard-dose images in the same patients (Table 2). These results and lower rate of dose reduction in comparison with other CAP studies may be correlated to a different level of strength of the iterative reconstruction of iDose^4 applied in our institution (L3) which determines less noise reduction and, with a fixed noise index, can be associated with higher levels of tube current and radiation dose.

The measured noise and SNR in low-dose images varied according to the weight of the patients, with higher values of SD and lower values of SNR in patients with higher weight (Table 3). These data were confirmed by qualitative analysis, which showed increasing levels of subjective noise by increasing patients weight, but without significant differences in image sharpness and diagnostic quality between the four groups (Table 2). In our patient group with weight greater than 90 kg (group D), values of SD within liver and spleen parenchyma and abdominal fat were the highest, with worst values of SNR; however, compared to standard-dose images, these values of SNR were higher indicating a better image contrast, although the difference was not statistically significant.

In group D the DLP reduction rate was substantially lower than those in the other patient groups (2.5% *vs* 29.6%, 33.5% and 29.9%). With automatic tube current modulation, tube current is automatically adjusted to the X-ray attenuation of the patient to keep the radiation dose as low as possible while maintaining a constant image noise level and specified image quality as in a previously defined reference image. In patients with large body habitus, to maintain a constant image quality, there is a risk of high radiation doses when this technique is applied in abdominal MDCT[23]. Our results could be explained then by the higher tube current needed and used in this group of patients to fulfill the fixed noise level and desired final image quality. In heavy patients, the optimal noise indexes and image quality should be adjusted to patient habitus, considering that subjective image quality in abdomen CT of these patients is usually higher because of the amount of fat deposition around the abdominal organ that improve tissue contrast[23].

There were several limitations in our study. First of all, it was a retrospective study and acquisition of CT paired studies in our patients were not realized on the same scanner; despite many technical parameters were identical between the two protocols, some of them and the scanners were different and it may have introduced some bias. Because of the interval time between studies, which was remarkable in a small number of patients, and the retrospective nature of the study, we couldn't compare conspicuity or detection rate of the primary tumor and secondary lesions between the two protocols, which should be addressed in further prospective studies.

In conclusion, in our sample of oncologic patients, automatic modulation of tube current and iDose^4 reconstruction algorithm allowed a mean radiation dose reduction of 28.9%, without significant loss of subjective diagnostic quality, and this protocol could be useful in reducing dose exposure in patients with malignancy which undergo a high number of chest-abdomen-pelvis CT scan during their clinical follow-up.

COMMENTS

Background

In the latest years, the number of computed tomography (CT) scans have increased significantly and this high number of examinations has raised concern because of the potential risk of radiation-induced malignancy. CT has a major role in the clinical management of patients with malignant diseases, which typically undergo multiple CT investigations during their follow-up, and risks derived from repeated scans and exposure to ionizing radiation should be balanced against the benefits of diagnostic imaging. On this basis in the study authors compared the diagnostic quality and the radiation dose of whole body CT scan examination obtained with a low-dose setting protocol combined with the new state of art iterative reconstruction algorithm with those obtained with a standard-dose protocol.

Research frontiers

New generation of high row number multidetector computed tomography (MDCT) scans allow thin-collimation, high spatial resolution and better multiplanar reconstructions (MPRs), and are increasingly used in clinical practice in oncologic field, because MDCT can assess in a single examination, the entire abdomen, pelvis and chest, allowing for local tumour staging and distant metastases evaluation. Several dose reduction tools are actually integrated in these new CT-scanners, including hardware components as dynamic helical collimator, adaptive axial collimator and tube-current modulation, and software post-acquisition improvements as iterative reconstruction algorithms. These technical solutions permit to reduce the dose delivered to the patients, maintaining high diagnostic quality of images.

Innovations and breakthroughs

CT protocols should be properly designed and carefully applied in order to obtain the highest amount of information by using the lowest radiation dose achievable, since the theoretical risk of radiation-induced cancer from CT examinations has been reported as not negligible. New CT scanners are equipped with several iterative reconstruction (IR) algorithms that allow a reduction of the radiation dose without theoretically affecting the image quality, especially if used in association with a low kV scanning protocol. The study was designed in order to obtain the best image quality with the lowest effective dose, using dose reduction strategies available with our scanner. iDose^4 is a fourth-generation hybrid IR algorithm introduced by Philips Healthcare, and the major component of this algorithm deals with subtraction of the image noise while

preserving the underlying edges associated with true anatomy or pathology.

Applications

In this study the authors compared radiation dose and image quality of CT examinations in a population of oncologic patients undergoing follow-up examinations with a new generation MDCT scanner (256-rows) using automatic modulation of current tube and iterative reconstruction algorithm (DoseRight system and iDose^4) and with a 16-MDCT scanner with standard dose protocol and FBP. The importance of this work relies on the fact that the results confirm the high diagnostic quality and the important radiation dose sparing of whole body CT scan examination obtained with a low-dose setting protocol combined with the new state of art iterative reconstruction algorithm in comparison with a standard-dose protocol. Moreover in this manuscript the authors compared and commented the results with those of previous literature on this field by using different vendor approach.

Terminology

MDCT: Multidetector row-CT are new generation of CT scanner with high number of detector, which allow to obtain high spatial resolution images with thinner collimation; FBP: Filtered back projection (FBP) has been the industry standard for CT image reconstruction for decades, representing a very fast and fairly robust method to reconstruct the raw data obtained from routinely CT scan acquisition; Hybrid Iterative Reconstruction Algorithms: In the literature, the term hybrid IR usually refers to algorithms that mainly decrease image noise by iterative methods. IR approaches are not new and were, in fact, the initially proposed method for data reconstruction in the early days of CT technology during the 1970s. However, due to its mathematically demanding properties and the large amount of data in CT imaging, until recently IR has not been practical for clinical purposes. The current evidence on the clinical implementation of IR into CT protocols shows substantial promise for major improvements in image quality, chiefly noise reduction-with subsequent radiation dose reduction-and artifact suppression; iDose^4: iDose^4 is a fourth-generation hybrid IR algorithm introduced by Philips Healthcare. With this algorithm the noise can be controlled for high spatial resolution reconstructions, hence providing high-quality, low-contrast, and spatial resolution within the same image, when radiologist work with low dose approach; through an iterative mathematical process, the noisy data are penalized and edges are preserved.

Peer-review

This is a very interesting attempt to achieve lower radiation dose in follow-up CT of oncologic patients with parallel comparison of thorax-abdomen-pelvis CT with 4th generation hybrid iterative reconstruction algorithm and standard dose examination.

REFERENCES

1 **Schauer DA**, Linton OW. NCRP Report No. 160, Ionizing Radiation Exposure of the Population of the United States, medical exposure--are we doing less with more, and is there a role for health physicists? *Health Phys* 2009; **97**: 1-5 [PMID: 19509507 DOI: 10.1097/01.HP.0000356672.44380.b7]

2 **Schauer DA**, Linton OW. National Council on Radiation Protection and Measurements report shows substantial medical exposure increase. *Radiology* 2009; **253**: 293-296 [PMID: 19864524 DOI: 10.1148/radiol.2532090494]

3 **Brenner DJ**, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007; **357**: 2277-2284 [PMID: 18046031]

4 **Padhani AR**. Imaging in the evaluation of cancer. In: Nicholson T (ed). Recommendations for cross-sectional imaging in cancer management, Second edition. London: The Royal College of Radiologists, 2014

5 **Williams S**. General techniques for examinations discussing CT, biopsy and MRI. In: Nicholson T, editor. Recommendations for cross-sectional imaging in cancer management, Second edition. London: The Royal College of Radiologists, 2014

6 **European Society of Radiology (ESR)**. White paper on radiation protection by the European Society of Radiology. *Insights Imaging* 2011; **2**: 357-362 [PMID: 22358387 DOI: 10.1007/s13244-011-0108-1]

7 **Tamm EP**, Rong XJ, Cody DD, Ernst RD, Fitzgerald NE, Kundra V. Quality initiatives: CT radiation dose reduction: how to implement change without sacrificing diagnostic quality. *Radiographics* 2011; **31**: 1823-1832 [PMID: 21969662 DOI: 10.1148/rg.317115027]

8 iDose4 iterative reconstruction technique, White Paper. Philips Healthcare, 2011

9 **Willemink MJ**, de Jong PA, Leiner T, de Heer LM, Nievelstein RA, Budde RP, Schilham AM. Iterative reconstruction techniques for computed tomography Part 1: technical principles. *Eur Radiol* 2013; **23**: 1623-1631 [PMID: 23314600 DOI: 10.1007/s00330-012-2765-y]

10 **Healthcare P**. The Brilliance iCT and DoseWise strategies. Healthcarepapers, 2009: 1-24

11 **Landis JR**, Koch GG. A one-way components of variance model for categorical data. *Biometrics* 1977; **33**: 67-679 [DOI: 10.2307/2529465]

12 **Arapakis I**, Efstathopoulos E, Tsitsia V, Kordolaimi S, Economopoulos N, Argentos S, Ploussi A, Alexopoulou E. Using "iDose4" iterative reconstruction algorithm in adults' chest-abdomen-pelvis CT examinations: effect on image quality in relation to patient radiation exposure. *Br J Radiol* 2014; **87**: 20130613 [PMID: 24646183 DOI: 10.1259/bjr.20130613]

13 **Karpitschka M**, Augart D, Becker HC, Reiser M, Graser A. Dose reduction in oncological staging multidetector CT: effect of iterative reconstruction. *Br J Radiol* 2013; **86**: 20120224 [PMID: 23255541 DOI: 10.1259/bjr.20120224]

14 **Prakash P**, Kalra MK, Kambadakone AK, Pien H, Hsieh J, Blake MA, Sahani DV. Reducing abdominal CT radiation dose with adaptive statistical iterative reconstruction technique. *Invest Radiol* 2010; **45**: 202-210 [PMID: 20177389 DOI: 10.1097/RLI.ob013e3181dzfeec]

15 **May MS**, Wüst W, Brand M, Stahl C, Allmendinger T, Schmidt B, Uder M, Lell MM. Dose reduction in abdominal computed tomography: intraindividual comparison of image quality of full-dose standard and half-dose iterative reconstructions with dual-source computed tomography. *Invest Radiol* 2011; **46**: 465-470 [PMID: 21467948 DOI: 10.1097/RLI.0b013e31821690a1]

16 **Chang W**, Lee JM, Lee K, Yoon JH, Yu MH, Han JK, Choi BI. Assessment of a model-based, iterative reconstruction algorithm (MBIR) regarding image quality and dose reduction in liver computed tomography. *Invest Radiol* 2013; **48**: 598-606 [PMID: 23511193 DOI: 10.1097/RLI.0b013e3182899104]

17 **Kaul D**, Grupp U, Kahn J, Ghadjar P, Wiener E, Hamm B, Streitparth F. Reducing radiation dose in the diagnosis of pulmonary embolism using adaptive statistical iterative reconstruction and lower tube potential in computed tomography. *Eur Radiol* 2014; **24**: 2685-2691 [PMID: 25007868 DOI: 10.1007/s00330-014-3290-y]

18 **Vardhanabhuti V**, Riordan RD, Mitchell GR, Hyde C, Roobottom CA. Image comparative assessment using iterative reconstructions: clinical comparison of low-dose abdominal/pelvic computed tomography between adaptive statistical, model-based iterative reconstructions and traditional filtered back projection in 65 patients. *Invest Radiol* 2014; **49**: 209-216 [PMID: 24368613 DOI: 10.1097/RLI.0000000000000017]

19 **Ren Q**, Dewan SK, Li M, Li J, Mao D, Wang Z, Hua Y. Comparison of adaptive statistical iterative and filtered back projection reconstruction techniques in brain CT. *Eur J Radiol* 2012; **81**: 2597-2601 [PMID: 22304977 DOI: 10.1016/j.ejrad.2011.12.041]

20 **Singh S**, Kalra MK, Shenoy-Bhangle AS, Saini A, Gervais DA, Westra SJ, Thrall JH. Radiation dose reduction with hybrid iterative reconstruction for pediatric CT. *Radiology* 2012; **263**: 537-546 [PMID: 22517962 DOI: 10.1148/radiol.12110268]

21 **Pontana F**, Duhamel A, Pagniez J, Flohr T, Faivre JB, Hachulla AL, Remy J, Remy-Jardin M. Chest computed tomography using iterative reconstruction vs filtered back projection (Part 2): image quality of low-dose CT examinations in 80 patients. *Eur Radiol* 2011; **21**: 636-643 [PMID: 21080171 DOI: 10.1007/s00330-010-1991-4]

22 **Hosch W**, Stiller W, Mueller D, Gitsioudis G, Welzel J, Dadrich M, Buss SJ, Giannitsis E, Kauczor HU, Katus HA, Korosoglou G. Reduction of radiation exposure and improvement of image quality with BMI-adapted prospective cardiac computed tomography and iterative reconstruction. *Eur J Radiol* 2012; **81**: 3568-3576 [PMID: 21784592 DOI: 10.1016/j.ejrad.2011.06.055]

23 **Schindera ST**, Nelson RC, Toth TL, Nguyen GT, Toncheva GI, DeLong DM, Yoshizumi TT. Effect of patient size on radiation dose for abdominal MDCT with automatic tube current modulation: phantom study. *AJR Am J Roentgenol* 2008; **190**: W100-W105 [PMID: 18212190 DOI: 10.2214/AJR.07.2891]

24 **Scharf M**, Brendel S, Melzer K, Hentschke C, May M, Uder M, Lell MM. Image quality, diagnostic accuracy, and potential for radiation dose reduction in thoracoabdominal CT, using Sinogram Affirmed Iterative Reconstruction (SAFIRE) technique in a longitudinal study. *PLoS One* 2017; **12**: e0180302 [PMID: 28678818 DOI: 10.1371/journal.pone.0180302]

25 **Bodelle B**, Isler S, Scholtz JE, Frellesen C, Luboldt W, Vogl TJ, Beeres M. Benefits of sinogram-affirmed iterative reconstruction in 0.4 mSv ultra-low-dose CT of the upper abdomen following transarterial chemoembolisation: comparison to low-dose and standard-dose CT and filtered back projection technique. *Clin Radiol* 2016; **71**: e11-e15 [PMID: 26521185 DOI: 10.1016/j.crad.2015.10.001]

26 **Song JS**, Lee JM, Sohn JY, Yoon JH, Han JK, Choi BI. Hybrid iterative reconstruction technique for liver CT scans for image noise reduction and image quality improvement: evaluation of the optimal iterative reconstruction strengths. *Radiol Med* 2015; **120**: 259-267 [PMID: 25168773 DOI: 10.1007/s11547-014-0441-9]

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CASE REPORT

Primary esophageal diffuse large B cell lymphoma presenting with tracheoesophageal fistula: A rare case and review

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Institutional review board statement: This case report does not require Texas Tech University Health Sciences Center IRB review.

Informed consent statement: Patient's legal guardian provided verbal informed consent authorizing discloses and use his information.

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Abstract

Primary non-Hodgkin lymphomas in the esophagus are rare. Tracheoesophageal fistulas mainly arise from solid esophageal carcinoma or mediastinal malignancies. Our patient presented with cough, dysphagia and weight loss, and upon initial computed tomography imaging and esophagogastroduodenoscopy, a malignant mass in the middle third of esophagus with tracheoesophageal fistula was found. The location of the mass and presence of malignant tracheoesophageal fistula were strongly suggestive of squamous cell carcinoma. However, tumor biopsy revealed diffuse large B-cell lymphoma. This case report details a rare incident of a primary diffuse large B-cell lymphoma presented as tracheoesophageal fistula and reviews previous literature.

Key words: Non-Hodgkin lymphoma; Tracheoesophageal fistula; Esophageal cancer; Esophageal lymphoma

Core tip: Primary non-Hodgkin lymphoma of esophagus is a rare disease, and tracheoesophageal fistula secondary to this condition prior to treatment is extremely rare and fatal. However, it has better prognosis than fistulas secondary to solid tumor if patients receive timely treatment.

Teerakanok J, DeWitt JP, Juarez E, Thein KZ, Warraich I. Pri-

mary esophageal diffuse large B cell lymphoma presenting with tracheoesophageal fistula: A rare case and review. *World J Gastrointest Oncol* 2017; 9(10): 431-435 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i10/431.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i10.431

INTRODUCTION

Lymphomas, the most common blood cancers, are characterized by proliferation of lymphocytes in the lymph nodes and of lymphoid tissue[1,2]. Lymphomas are categorized into two groups: Hodgkin and non-Hodgkin lymphomas (NHLs). Among NHLs, diffuse large B-cell lymphomas (DLBCLs) account for 40% of all lymphoma cases worldwide[3]. Primary gastrointestinal (GI) lymphoma is the most common extranodal presentation NHL; however, most cases involve the stomach, small intestine and colon. Esophageal involvement is the rarest. Malignant tracheoesophageal fistula (TEF) from NHL is uncommon and presents mostly as complication of radiation therapy or chemotherapy.

Here, we present a rare case of a primary esophageal NHL presented with malignant TEF. To the best of our knowledge, this is the first case of primary DLBCL with malignant TEF prior to cancer treatment.

CASE REPORT

A 60-year-old male with past medical history of diabetes mellitus type 2, hypothyroidism and chronic tobacco smoking presented with gradually worsening 3-wk dry cough, dysphagia and cough provoked with all oral intake. On review of systems, patient had unintentional 30-pound weight loss in the past 3 mo. On physical exam vital signs were unremarkable except for oxygen saturation of 91% on room air with respiratory rate of 18 breaths per minute. Moreover, the patient was not in acute distress; his breathing was non-labored; liver and spleen were not palpable; superficial lymphadenopathy was not found. The initial CBC revealed a white blood cell count of 21900/μL, 5% bands, 81% segmented neutrophils, 5% lymphocyte, and 8% monocytes. Lactate dehydrogenase was 223 units/L (normal value; 135-225 units/L), liver functions and renal functions were unremarkable and human immunodeficiency virus (HIV) was negative. A chest computed tomography (CT) imaging revealed a mid-esophageal wall thickening and enhancement, a fistulous connection between the membranous portion of the trachea and the anterior portion of the mediastinum, nonspecific mediastinal lymph nodes enlargement and some of ground glass opacity in posterior segment of the upper lobes and superior segments of the lower lobes bilaterally (Figure 1). Abdominal and pelvic CT imaging revealed multiple lytic lesions in pelvic bone, mild hepatic steatosis, normal spleen and no intraabdominal or pelvic lymphadenopathy. Our patient was started on levofloxacin for concern of aspiration pneumonia.

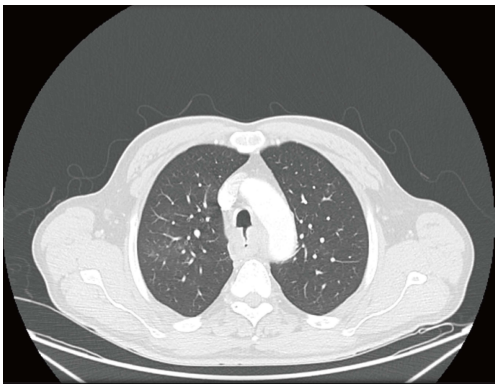

Figure 1 Contrasted chest computed tomography imaging showing tracheo-esophageal fistula in a 60-year-old male patient.

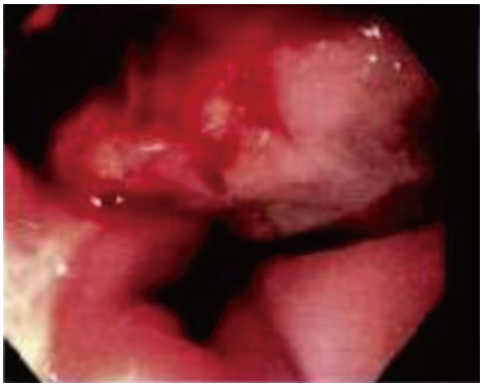

Figure 2 Esophagogastroduodenoscopy showing a partially obstructing mid-esophageal tumor and tracheoesophageal fistula in a 60-year-old male patient.

Esophagogastroduodenoscopy (EGD) found a large fungating and ulcerating mass in the middle third of the esophagus with partial obstruction, and TEF was found in the middle third of the esophagus with tracheal rings (Figure 2). Bronchoscopy revealed 3 cm TEF in the trachea and 1.5 cm bronchoesophageal fistula in left mainstem. The esophageal mass biopsy showed large, highly pleomorphic cells with diffuse growth pattern (Figure 3A). Various immunohistochemical staining were performed. Tumor cells had strong and diffuse expression for CD20 (Figure 3B), CD10, CD45, CD79a and bcl2. CD 3 and CD5 were negative. Cytokeratin (CK) AE1/AE3 was negative for the cells of tumor infiltrate (Figure 3C). Tumor cells did not show any expression for P40, a marker for squamous cell carcinoma (Figure 3D). These findings were consistent with diffuse large B-cell lymphoma diagnosis. Bone marrow biopsy was not performed because CT imaging suggested bone marrow involvement. Lumbar puncture was not done as well. Patient underwent for percutaneous endoscopic gastrostomy tube placement, esophageal stent placement and tracheobronchial stent placement. He received rituximab 375 mg/m^2 for 1 dose, and a week later he subsequently received complete first cycle of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP regimen). Patient completed 6

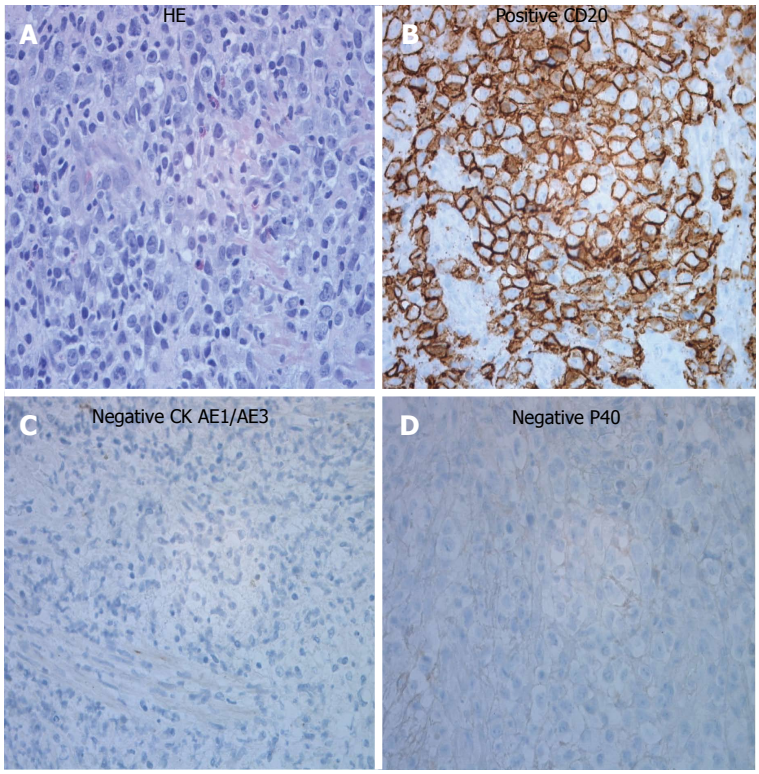

Figure 3 Histological features of primary diffuse large B-cell lymphoma in a 60-year-old male patient. A: HE staining shows highly pleomorphic large cell proliferation on sections of neoplasm; B: Immunohistochemistry shows tumor cells with a strongly diffused positive expression for CD20; C: Cytokeratin (CK) AE1/AE3 was negative for the cells of tumor infiltrate; D: P40 was negative for squamous carcinoma.

cycles of R-CHOP with good response in tumor but still has persistent TEF with intermittent aspiration. He lost 30 pounds during the course of treatment due to poor feeding intolerance.

DISCUSSION

GI lymphomas comprise 5%-20% of extranodal lymphomas[4] and only 1%-4% of all GI cancers[5]. Primary esophageal lymphoma accounts for less than 1% of GI lymphomas. The earliest reported primary esophageal NHL was in 1979[6]. Heretofore, there have been less than 25 reported cases of primary esophageal cancer from NHL[7-16]. Sometimes, it can be difficult to differentiate between primary GI lymphomas and lymphomas that disseminated to GI tract. Dawson *et al*[17] described the diagnostic criteria of primary GI lymphomas: (1) absence of peripheral lymphadenopathy; (2) absence of mediastinal adenopathy; (3) no involvement of liver and spleen; and (4) normal peripheral blood count. Majority of primary GI lymphomas are DLBCL[18]. A major risk factor for primary esophageal lymphoma is immunosuppression, such as HIV infection[19]. Radiologic features of primary esophageal lymphoma are ulceration, stenosis, polypoid masses, aneurysmal dilatation and TEF, which are non-specific[19,20].

Malignant TEF is a serious late complication of cancers. Most malignant TEF cases are related to esophageal and lung cancers[21]. TEF from primary esophageal lymphoma is an uncommon complication. TEF in lymphoma frequently develops during or after treatment with radiation or chemotherapy, but it can occur due to the disease itself. Most of the reports were of Hodgkin lymphomas[22-25]. Even though literature review reveals case reports of NHL with esophageal-tracheobronchial connection, the reported NHLs are not primary esophageal NHLs[26-28]. Malignant TEF usually has very poor prognosis; however, if lymphomas are recognized and treated early, TEF repair and chemotherapy treatment will result in good prognosis[29]. Standard treatment of DLBCL is R-CHOP regimen. Management of TEF is predominantly a non-surgical intervention because of the difficulty of and risk from surgery. Esophageal stent and/or airway stent is effective to prevent aspiration of GI contents and risk of pneumonia. In addition, general treatments, such as gastrostomy/jejunostomy tube, antibiotics and airway secretion prevention help reduce further risk of aspiration[22,30].

Novelty of this case report is the co-presence of malignant TEF with primary DLBCL in the esophagus. Primary esophageal lymphoma-related TEF is extremely rare but fatal. Physicians should suspect it for timely diagnosis since NHL with TEF has better prognosis with interventions and chemotherapy alone than TEFs caused by esophageal cancer or lung cancer.

COMMENTS

Case characteristics

A 60-year-old man presented with worsening 3-wk dry cough, dysphagia and cough provoked with all oral intake.

Clinical diagnosis
Clinical examination was unremarkable.

Differential diagnosis
Stroke, esophageal spasm, esophageal tumor, tracheoesophageal fistula-related or pulmonary infection.

Laboratory diagnosis
Blood count showed leukocytosis suggested of infection or inflammation, but lactate dehydrogenase andliver function were unremarkable.

Imaging diagnosis
Chest, abdominal and pelvic computed tomography imaging revealed fungating and ulcerating mass in the middle third of the esophagus with partial obstructionand tracheoesophageal fistula (TEF) without significant lymphadenopathy.

Pathological diagnosis
Esophageal mass biopsy revealed diffuse large B-cell lymphoma.

Treatment
Patient received chemotherapy R-CHOP regimen and underwent to have PEG tube placement, tracheal and esophageal stents.

Related reports
Most primary esophageal lymphoma cases are the rarest among primary gastrointestinal lymphoma, and TEF is seldom found as a presenting symptom.

Term explanation
Tracheoesophageal fistula is an abnormal connection between the esophagus and trachea. Diffuse large B cell lymphoma is a subtype of non-Hodgkin lymphoma.

Experiences and lessons
Primary esophageal lymphoma is extremely rare, and malignant TEF is fatal. However, patients with this condition have better prognosis if they receive a proper management.

Peer-review
This case report is very interesting and rare. It is helpful to know if the patient has been immunologically investigated. The manuscript is well written and illustrations are informative.

REFERENCES

1 **Perry RR**, Rosenberg RK, Pass HI. Tracheoesophageal fistula in the patient with lymphoma: case report and review of the literature. *Surgery* 1989; **105**: 770-777 [PMID: 2471284]
2 **Perry AM**, Diebold J, Nathwani BN, MacLennan KA, Müller-Hermelink HK, Bast M, Boilesen E, Armitage JO, Weisenburger DD. Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. *Haematologica* 2016; **101**: 1244-1250 [PMID: 27354024 DOI: 10.3324/haematol.2016.148809]
3 **Caimi PF**, Hill BT, Hsi ED, Smith MR. Clinical approach to diffuse large B cell lymphoma. *Blood Rev* 2016; **30**: 477-491 [PMID: 27596109 DOI: 10.1016/j.blre.2016.06.003]
4 **Freeman C**, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972; **29**: 252-260 [PMID: 5007387]
5 **Gurney KA**, Cartwright RA. Increasing incidence and descriptive epidemiology of extranodal non-Hodgkin lymphoma in parts of England and Wales. *Hematol J* 2002; **3**: 95-104 [PMID: 12032871 DOI: 10.1038/sj/thj/6200154]
6 **Berman MD**, Falchuk KR, Trey C, Gramm HF. Primary histiocytic lymphoma of the esophagus. *Dig Dis Sci* 1979; **24**: 883-886 [PMID: 520110]
7 **Chadha KS**, Hernandez-Ilizaliturri FJ, Javle M. Primary esophageal lymphoma: case series and review of the literature. *Dig Dis Sci* 2006; **51**: 77-83 [PMID: 16416216 DOI: 10.1007/s10620-006-3088-0]
8 **Doki T**, Hamada S, Murayama H, Suenaga H, Sannohe Y. Primary malignant lymphoma of the esophagus. A case report. *Endoscopy* 1984; **16**: 189-192 [PMID: 6489278 DOI: 10.1055/s-2007-1018579]
9 **Ghimire P**, Wu GY, Zhu L. Primary esophageal lymphoma in immunocompetent patients: Two case reports and literature review. *World J Radiol* 2010; **2**: 334-338 [PMID: 21160688 DOI: 10.4329/wjr.v2.i8.334]
10 **Gupta NM**, Goenka MK, Jindal A, Behera A, Vaiphei K. Primary lymphoma of the esophagus. *J Clin Gastroenterol* 1996; **23**: 203-206 [PMID: 8899502]
11 **Kim Jh**, Jung Yh, Woo IS, Ha SY. Two Cases of Primary Esophageal Diffuse Large B Cell Lymphoma: Therapeutic Considerations and a Literature Review. *Korean J Med* 2015; **88**: 224-230 [DOI: 10.3904/kjm.2015.88.2.224]
12 **Matsuura H**, Saito R, Nakajima S, Yoshihara W, Enomoto T. Non-Hodgkin's lymphoma of the esophagus. *Am J Gastroenterol* 1985; **80**: 941-946 [PMID: 4073001]
13 **Mengoli M**, Marchi M, Rota E, Bertolotti M, Gollini C, Signorelli S. Primary non-Hodgkin's lymphoma of the esophagus. *Am J Gastroenterol* 1990; **85**: 737-741 [PMID: 2353695]
14 **Sabljak P**, Stojakov D, Bjelovic M, Mihaljevic B, Velickovic D, Ebrahimi K, Spica B, Pesko P. Primary esophageal diffuse large B-cell lymphoma: report of a case. *Surg Today* 2008; **38**: 647-650 [PMID: 18612792 DOI: 10.1007/s00595-007-3690-6]
15 **Tsukada T**, Ohno T, Kihira H, Taniguchi M, Takahashi T, Arima S, Yamada H, Akasaka Y, Yokoi H, Kita K. Primary esophageal non-Hodgkin's lymphoma. *Intern Med* 1992; **31**: 569-572 [PMID: 1633371]
16 **Ximenes M**, Piauilino MA, Oliveira HA, Vaz Neto JP. [Primary esophageal lymphoma]. *Rev Col Bras Cir* 2012; **39**: 243-246 [PMID: 22836576]
17 **Dawson IM**, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *Br J Surg* 1961; **49**: 80-89 [PMID: 13884035]
18 **Howell JM**, Auer-Grzesiak I, Zhang J, Andrews CN, Stewart D, Urbanski SJ. Increasing incidence rates, distribution and histological characteristics of primary gastrointestinal non-Hodgkin lymphoma in a North American population. *Can J Gastroenterol* 2012; **26**: 452-456 [PMID: 22803021]
19 **Tirumani H**, Rosenthal MH, Tirumani SH, Shinagare AB, Krajewski KM, Ramaiya NH. Imaging of uncommon esophageal malignancies. *Dis Esophagus* 2015; **28**: 552-559 [PMID: 24635682 DOI: 10.1111/dote.12208]
20 **Carnovale RL**, Goldstein HM, Zornoza J, Dodd GD. Radiologic manifestations of esophageal lymphoma. *AJR Am J Roentgenol* 1977; **128**: 751-754 [PMID: 404896 DOI: 10.2214/ajr.128.5.751]
21 **Rodriguez AN**, Diaz-Jimenez JP. Malignant respiratory-digestive fistulas. *Curr Opin Pulm Med* 2010; **16**: 329-333 [PMID: 20531081 DOI: 10.1097/MCP.0b013e3283390de8]
22 **Westin JR**, Gibbs A, Mills KR, Neelapu SS. Hodgkin lymphoma untreated for six years presenting with tracheoesophageal fistula. *Case Rep Med* 2012; **2012**: 457908 [PMID: 22811723 DOI: 10.1155/2012/457908]
23 **Kutchuk M**, Edelstein Y, Ellis MH. Late relapse of Hodgkin's lymphoma presenting as fatal hematemesis caused by an esophago-tracheo-arterial fistula. *Isr Med Assoc J* 2009; **11**: 637-638 [PMID: 20077955]
24 **Coppens E**, El Nakadi I, Nagy N, Zalcman M. Primary Hodgkin's lymphoma of the esophagus. *AJR Am J Roentgenol* 2003; **180**: 1335-1337 [PMID: 12704047 DOI: 10.2214/ajr.180.5.1801335]
25 **Alba D**, Lobato SD, Alvarez-Sala R, Villasante C, Echevarría C. Tracheoesophageal fistula as the presenting manifestation of Hodgkin's lymphoma. *Postgrad Med J* 1994; **70**: 49-50 [PMID: 8140022]
26 **Sharma M**, Aronow WS, O'Brien M, Gandhi K, Amin H, Desai H. T cell lymphoma presenting as esophageal obstruction and bronchoesophageal fistula. *Med Sci Monit* 2011; **17**: CS66-CS69 [PMID: 21629192]

27 **Sawyer R**, Rosenthal DI, Maniglia AJ, Goodwin WJ. Unusual head and neck manifestations of non-Hodgkin's lymphomas in children and adults. *Laryngoscope* 1987; **97**: 1136-1140 [PMID: 3657359]
28 **Joshi A**, Fields P, Simo R. Anaplastic lymphoma of the cervical esophagus presenting as a tracheoesophageal fistula. *Head Neck* 2008; **30**: 1264-1268 [PMID: 18228520 DOI: 10.1002/hed.20774]
29 **Gschossmann JM**, Bonner JA, Foote RL, Shaw EG, Martenson JA Jr, Su J. Malignant tracheoesophageal fistula in patients with esophageal cancer. *Cancer* 1993; **72**: 1513-1521 [PMID: 7688653]
30 **Ke M**, Wu X, Zeng J. The treatment strategy for tracheoesophageal fistula. *J Thorac Dis* 2015; **7**: S389-S397 [PMID: 26807286 DOI: 10.3978/j.issn.2072-1439.2015.12.11]

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