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Evaluating long-term attachment of two different endoclips in the human gastrointestinal tract

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ABSTRACT

BACKGROUND

The spectrum of clinical indications for the use of endoscopic clips (endoclips) is rapidly expanding. As retention rates of endoclips have only been reported in animal models, we evaluated the long-term attachment of two types of endoclips in the human gastrointestinal tract.

METHODS

In this prospective observational study, endoclips were placed and followed-up during endoscopies or using fluoroscopic images as part of a prospective feasibility study evaluating external beam radiotherapy (EBRT, wk 1-3) followed by high dose rate brachytherapy (HDRBT with an endoluminal applicator once a week for three weeks, wk 9-11) in medically inoperable rectal cancer patients. Initially, type and number of endoclips were chosen randomly and later refined to 1 Resolution® clip (Microvasive) proximal and 2 Quickclips® (Olympus) distal to the tumour. Nine consecutive patients, included between September 2007 and August 2008, were analysed. Retention rates were evaluated over three different observational periods (period 1: pre-HDRBT (wk -2 - 8), period 2: during HDRBT (wk 9-11) and period 3: post-HDRBT (wk 12-16).

RESULTS

In this study a total of 44 clips were placed during endoscopy, either at the beginning or at the end of period 1. The Resolution clip had a higher overall retention rate than the Quickclip (P = 0.01). After a median period of 81 days after placement (in period 1), long-term retention rates for the Resolution clip and Quickclip clip were 67% and 35%, respectively.

CONCLUSION

The Resolution clip has a high retention rate and is useful in situations where long-term attachment to the human gastrointestinal mucosa is warranted.
INTRODUCTION

In 1975, Hayashi et al were the first to describe the metallic endoscopic clip as an alternative means to control bleeding by mechanical pressure\(^1\). Since then, design and clinical indications have been refined. Nowadays, endoscopic clips are frequently used for haemostasis of arterial non-variceal bleeding of the upper gastrointestinal tract\(^2\). Other reported indications for endoscopic clip placement include the fixation of enteral feeding tubes\(^3\), stent anchorage\(^4\) and the management of small fistulas, perforations and anastomotic leaks\(^5\). Utilizing their radiopaque characteristics, endoclips have recently been used to mark tumours or anatomical structures to facilitate intervention radiology\(^6\), to locate the tumour peroperatively\(^7\) and to delineate tumour volume for radiotherapy\(^8,9\).

Several types of endoscopic clips are commercially available. Most studies involve those from Olympus (Olympus Ltd., Tokyo, Japan), available in preloaded (Quickclip) and reloadable devices (HX-5L). Once the clip has been opened, re-positioning is not possible as the jaws cannot be closed and reopened. The Resolution clip (Microvasive, Boston Scientific Corp, Massachusetts, US) has the ability to reopen its jaws for repositioning, which may result in superior positioning and tissue grasping.

The ability of an endoclip to remain attached for a longer period could facilitate procedures in which a tumour needs to be located routinely during the treatment period or when the clip anchors feeding tubes or stents. Retention rates have, however, only been evaluated in canines and pigs and have not yet been reported in the human gastrointestinal tract. The aim of this study was to evaluate the long-term attachment of two endoclips, the Quickclip and the Resolution clip, to human rectal mucosa.

MATERIAL AND METHODS

STUDY POPULATION

The 9 consecutive patients analysed in this study were patients with medically inoperable rectal cancer who participated in a prospective feasibility study in the Netherlands Cancer Institute. The primary objective of this on-going study is to evaluate the feasibility of external beam radiation therapy (EBRT) followed by high-dose rate endorectal brachytherapy (HDRBT) as definitive treatment in patients not suitable for surgery due to co-morbidity, old age or for those refusing surgery. The study gained ethical approval from the Medical Ethics Committee of the Netherlands Cancer Institute. Written informed consent was obtained from all patients. Patient accrual commenced in September 2007.

TREATMENT PROTOCOL

The treatment regimen (Figure 1) consists of 39 Gy administered in 13 fractions of 3 Gy over 3½ weeks. After a further six weeks, HDRBT is applied once every week for three weeks. HDRBT dose level will be elevated (starting at 5 Gy/fraction) after every 6 patients depending on experienced toxicity. HDRBT is applied using an endorectal applicator (Oncosmart®, Nucletron, Veenendaal, the Netherlands).
consisting of a flexible tube with 8 channels (Figure 2). The applicator is 2 cm in diameter and is inserted via the anus prior to each brachytherapy treatment.

Figure 1: Treatment plan: Patients first receive external beam radiotherapy followed by high dose rate brachytherapy. Abbreviations: EBRT: external beam radiotherapy. HDRBT: high dose rate brachytherapy. wk: week

ENDOCLIPS

The rectal tumour was marked (Figure 3a) with Quickclips (Olympus Ltd., Tokyo, Japan) and/or Resolution (Microvasive, Boston Scientific Corp, Massachusetts, US) endoclips to facilitate tumour localization during the HDRBT procedure. Endoscopy was performed before EBRT (baseline), before HDRBT (week 8-9) and after HDRBT (week 16-17). The tumour was marked before EBRT and, if necessary, additionally (when clips had been dislodged) before HDRBT. Initially, type and number of endoclips were chosen randomly. Later on, this was refined to one Resolution endoclip at the proximal and two Quickclips at the distal border of the tumour.

Figure 2: Depicts the endorectal applicator (Oncosmart®, Nucletron, Veenendaal, the Netherlands) used to apply High Dose Rate Brachytherapy.
Evaluating long-term attachment of two different endoclips in the human gastrointestinal tract

TREATMENT PLANNING

A CT-scan, with the unloaded applicator inserted, was performed for delineation and treatment planning purposes before the first HDRBT fraction. A 3D reconstruction of the applicator and radio-opaque endorectal clips was made and the target volume delineated on the CT-images. A 2D anterior-posterior projection of applicator and clips was reconstructed as a reference for C-arm fluoroscopy guided reinsertion of the applicator prior to each HDRBT session (week 9-11, Figure 3b).

DATA ANALYSES

We evaluated retention rates between the two clip types over three different observational periods (period 1: pre-HDRBT (week -2 - 8), period 2: during HDRBT (week 9-11) and period 3: post-HDRBT (week 12-16)) (Figure 1). The percentage and absolute number of clips still attached during follow-up endoscopy and on the fluoroscopic images were determined. To assess the retention rates of the two clip types (Quickclip or Resolution) a logistic mixed effects model was constructed with clip type as a fixed effect. To account for the influence of both the different periods (different in length and use of an endoluminal applicator) and the duration of attachment prior to assessment we included placement (beginning of period 1 or 2) and assessment period as fixed effects. The assessments of clip retention was assumed to be correlated when they relate to the same clip (assessed for different periods) or from clips within the same patient. To account for this cluster correlation we included clip and patient id as random intercepts. Due to insufficient events in period 2 a logistic model was unable to be constructed; hence the comparison of the retention rates of the two clip types in this period was performed using a Mantel-Haenszel test. Where appropriate, two-sided p-values are reported with a significance level set at 0.05.

Figure 3 Imaging of the endoclips: A) Shows endoscopic images of an attached Resolution clip on the left (with a recognizable silver part at the loose end) and 2 attached Quickclips on the right (with a recognizable silver part at the centre of the clip).
RESULTS

Six male and three female patients were evaluated. Median age of patients was 81 (range 57-93) years. Seven of the nine patients completed the treatment. One patient did not receive HDRBT after the EBRT due to an ulcer located in the brachytherapy field, while the other patient not completing treatment died due to a non-treatment related cardiac arrest after the first HDRBT treatment. Retention rates for the different observational periods are depicted in Table 1.

In this study a total of 44 clips were placed during endoscopy, either at the beginning or at the end of period 1. At the beginning of period 1 (before EBRT), 26 clips were placed. The median duration of period 1 was 81 (49-90) days. Of the 20 Quickclips placed, 7 (35%) were visualized during the follow-up endoscopy at the end of period 1. Four of the 6 (67%) Resolution clips placed were visualized at this second endoscopy. During the same endoscopy at the end of period 1, 18 clips were additionally placed (15 Quickclips and 3 Resolution clips) to replace dislodged clips. Median time between placement/visualization at the end of period 1 and the next follow-up endoscopy (end of period 3) was 72 (range 33-91) days. No Quickclips survived all three periods, while 1 additionally placed Quickclip was visualized at the end of period 3. One of the 6 Resolution clips placed at the beginning of period 1 survived all three periods and was still visible at last follow-up after 231 days. One of the 3 additionally placed Resolution clips was visualized at the end of period 3 as well. Therefore, at the follow-up endoscopy after HDBRT (end of period 3), 1 (7%) Quickclip and 2 (40%) Resolution clips were visualized.
Table 1: Clip retention rates over three periods.

<table>
<thead>
<tr>
<th>Period</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
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<tr>
<td></td>
<td>During 2nd endoscopy (Before HDRBT, after EBRT)</td>
<td>Images after week 1 (During HDRBT)</td>
<td>Images after week 2 (During HDRBT)</td>
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<td>Resolution (visualized/placed\textsuperscript{a})</td>
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<td>Total</td>
<td>7/20 (35%)</td>
<td>4/6 (67%)</td>
<td>16/20\textsuperscript{f} (80%)</td>
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Superscripts: a: “Placed” includes those clips placed during the first endoscopy. b: “Placed” includes those clips that were placed at the 2nd endoscopy but also those (7 Quickclips and 4 Resolution) that were still attached from the 1st endoscopy. c: “Placed” are the number of clips at last visualization in period 2 (for patient 5 this is during placement during period 2). d: This patient died due to a sudden cardiac arrest during the HDRBT. e: Due to missing images of patient 5, the 2 placed Quickclips and 1 resolution clip were excluded from the analysis in the corresponding period. Abbreviations: EBRT: external beam radiotherapy, HDRBT: high dose rate brachytherapy.
Retention rates gathered from the fluoroscopy images, acquired every week during the HDBRT, are depicted in Table 1. After 1, 2 and 3 weeks, these were 80%, 60% and 63% for the Quickclips versus 83%, 80% and 75% for the Resolution clip. In case no image was available, the clip was censored which explains why the 3 week Quickclip retention rate is higher than the 2 week rate. The retention rates after 1, 2 and 3 weeks in period 2 did not differ significantly between the 2 types of clips (p=0.17, Mantel Haenszel test). The Resolution clip had a higher overall retention rate than the Quickclip [Odds Ratio: 96 (2.5-3614), p=0.01]. In comparison to the first period, long-term retention rates deteriorated significantly in the third period when the endoluminal applicator had been inserted [Odds Ratio: 0.01 (0.0003-0.2), p=0.003].

**DISCUSSION**

In this study, we found the Resolution clip to be superior to the Quickclip in situations where long-term attachment is warranted. The Resolution clip remained attached longer than the Quickclip, with encouraging long-term retention rates of up to 67% for the Resolution clip after nearly 12 weeks. In contrast, only 35% of the Quickclips remained attached.

Recently, Eun Ji Shin et al compared the attachment duration of two endoscopic clips (the Quickclip’s predecessor, the HX-5L, versus the Resolution clip) in the gastric mucosa of 5 pigs. They also found that the Resolution clip had the longest rate of retention, being visualized during follow-up endoscopy after 1, 2 and 4 or 5 weeks (range of retention rates: 4-5 weeks) and concluded that it be preferred over the HX-5L clip (80% dislodged within 2 weeks) when long-term attachment is important. Similar results were reported in a randomized controlled study of 3 types of endoscopic clips used for haemostasis in bleeding gastric ulcers in 7 canines. In their study, the median clip retention time was 2 weeks for the Quickclip (maximum duration of attachment of 3 weeks) and 4 weeks for the Resolution clip (maximum duration of attachment of 18 weeks). The nature of our study enabled the first report in humans in vivo and is in line with these reports, favouring the Resolution clip when long-term attachment is required. Furthermore, we describe retention after almost 12 weeks follow-up. Long-term attachment of an endoscopic clip was first described in 1994 when Iida et al reported clip retention (HX-3L, Olympus, total number of clips placed unknown) of up to 26 months after placement in a patient during a colonoscopic polypectomy. In our study, 1 Resolution clip was even visualized 33 weeks after placement, while the longest measured attachment of a Quickclip was 15 weeks. Clinical indications that would benefit from long-term attachment include the fixation of stents and feeding tubes in the oesophagus and bowel, respectively.

Regarding the effect of mechanical exertion on the endoscopic clips, we found the following: overall, the resolution clip survived the continuous passing of stools more effectively than the Quickclip. However, in our study, the retention rates of both the Resolution clip and the Quickclip deteriorated during the second and third period (during and after HDBRT) in comparison to the first period, where patients underwent external beam radiotherapy (Table 1). As suggested earlier, one probable cause for this decreased retention is the fact that an endorectal brachytherapy applicator was placed in the
second period in order to plan and perform the HDBRT (4 times in total), which could have mechanically dislodged both types of clips in the process. Another plausible reason could be that some of the clips (7 Quickclips and 4 Resolution clips) evaluated in period 2 were placed during the first endoscopy. With a grip that theoretically deteriorates due to cell renewal and mechanical pressure of passing stools during defecation, these clips could possibly have been on the verge of dislodgement, leading to the decreased retention rate over periods 2 and 3. Regarding the subgroup of endoscopic clips in our study in which attachment was determined after 1, 2 and 3 weeks, retentions rates (Table 1) are at least in line with those reported in the abovementioned study by Jensen et al (Quickclip: 74%, 30% and 11% versus the Resolution clip: 65%, 58% and 45% after 1, 2 and 4 weeks). Interestingly, when one only looks at the retention of the two clip types during these periods (at 1, 2 and 3 weeks) in our study the Quickclip retention rate did not significantly differ from that of the Resolution clip (p=0.17). That in contrast to what Jensen et al describes, although this could be due to a lack of power for this sub-group analysis in our study. Our result implies that short-term attachment directly after external mechanical exertion (endorectal applicator) is not significantly superior for the Resolution clip, but that does seem to be the case in the period thereafter in which 40% of Resolution clips were visualized, versus 7% of the Quickclips. This suggests that if the clip survives the applicator, the Resolution clip seems to survive longer.

Finally, we found the endoscopic clips to be useful in locating and marking the tumour borders for radiotherapy volume delineation and for optimizing the position of the endorectal brachytherapy applicator. Pfau et al recently reported similar promising results in optimizing radiotherapy volume delineation in oesophageal cancer patients. However, a possible downside for the clinical use of endoclips is the fact that they are not MRI-compatible, having caused artefacts on MRI in our series.

In conclusion, in this small prospective study we evaluated long-term attachment of the Quickclip and the Resolution clip to human rectal mucosa. We found that up to two thirds of Resolution clips were visualized at follow up after a median of nearly 12 weeks illustrating their superior value in situations where long term attachment is warranted.