Review Article

Esophageal stents: Beyond the simple stricture

Derek William Edwards, Hans-Ulrich Laasch*

Abstract

Advances in chemo-radiotherapy and cancer surgery are changing the landscape of esophageal stent insertion. Where previously patients received stents for end-stage esophageal carcinoma with a poor prognosis, long-term survival is beginning to become the norm. In addition more patients are undergoing radical surgery and consequently more patients are presenting with disease relapse in altered anatomy. Furthermore, patients with extra-esophageal cancer can require stent insertion, but their underlying disease may run a different course from esophageal cancer. We illustrate the challenges for stent performance, material longevity and forward thinking of the operator presented by the change in disease spectrum and behavior.

Keywords: Complications; Endoscopy; Esophageal neoplasms; Palliative medicine; Radiology, interventional

Introduction

Esophageal stents are increasingly applied outside the original indication of palliating obstruction by terminal esophageal cancer. With wider use have come increasing challenges to the materials and the construction of esophageal stents. Requirements for improved performance may come from surgically altered anatomy, external compression, fistulae in the absence of a stricture and increasingly by improved patient survival. The UK Registry of Oesophageal Stenting (ROST) documented average survival of 92 days in 2004. However, with improvement of palliative chemo-radiotherapy regimes, it is now not unusual for patients to survive years rather than months after receiving an esophageal stent. This applies particularly to patients who had esophageal involvement or compression from breast and lung cancer. In these tumor groups, advances in oncological treatment have been particularly successful and patient survival of several years—even with metastatic disease—is increasingly the norm. The resulting requirements for reliable long-term performance and stent integrity are probably the greatest challenge for current stent technology.

Firstly, extended exposure to gastric acid seems to play an important role in stent degradation and resultant fracture. Disintegration of the metal stent skeleton and/or the covering membrane results in stent failure and can make re-intervention very difficult. Although initially attributed to disruption of the membrane connecting separate stent segments fractures of the nitinol skeleton is not infrequent in long-term survivors. This is most commonly observed with stents placed within the stomach or at the cardia and the gastric outlet and gastric acid is a likely precipitating factor. Signs of stent failure are usually evident on standard computed tomography (CT) scans performed to assess treatment response. However, these may be easily be missed by radiologists not involved in intervention. Diagnosis is important as even subtle, early stent fractures may lead to significant functional impairment (Fig. 1). Re-intervention in fractured stents has to be considered very carefully. Attempts at removal may disrupt the stent or cause laceration of the esophagus. Insertion of a further stent may result in this being placed through the interstices of the damaged stent and a potentially irretrievable disaster in terms of function.

Secondly, a reduction in tumor bulk from palliative treatment leads to reduced stent fixation and increased stent migration and the subsequent difficult decision whether an attempt should be made to remove a migrated stent.

Special Situations

Cervical esophagus

Stent placement in the cervical esophagus for high strictures is difficult, as patient awareness of the stent increases with proximity to the cricopharyngeus (CPS) muscle. High strictures may
preclude endoscopy and radiological guidance is preferable. CPS is normally identified at the level of C5 to C6 at videofluoroscopy. Stents can usually be placed successfully with their upper end at the top of C7 vertebral body, approximately 2 to 3 cm below CPS. If placed above that level the facility to remove the stent within 24 hours must be available, in case the patient cannot tolerate the stent.

A number of stents have been developed that have either a shortened flare at the proximal end, a smaller diameter or a proximal end with reduced expansion force (Fig. 2), which may improve tolerance.\(^5\)\(^,\)\(^6\) Accurate placement of the proximal end is crucial in these cases and a forward deploying (“push”) delivery system allows greater control over the final position of the proximal end (Fig. 3). The same can be achieved via a retrograde approach through an existing gastrostomy.

For large tumors in the cervical esophagus, particularly if the trachea is involved, stenting may result in tracheal compression. If there is tumor extension into the airway or stridor, a tracheal stent must be inserted first.

---

**Fistula without stricture**

One of the most challenging scenarios for esophageal stenting is a hole in the esophagus requiring closure, but without associated stricture to fix the stent. In a malignant context this is most likely due to invasion of the esophagus from an external bronchial carcinoma. Fistulae may occur primarily or as a consequence of successful radiotherapy. The prognosis in these patients is usually poor, but failure to close the fistula shortens survival.\(^7\) Occluding the esophageal side is preferable to attempts at closure of the tracheal side alone,\(^8\) but most esophageal stents are not suitable for application in this context, as they rely on fixation by an associated stricture. This may be achieved by partially covered stents (Fig. 4A), which allow embedding of the uncovered segments in the esophageal mucosa, but this renders them not removable. One dedicated stent for benign esophageal perforations exists (Danis Seal; Ella-CS, Hradec Králové, Czech Republic; Fig. 4B). This consists of an extra-large 25 mm trunk flaring to 30 mm, which increases the fixation force on the esophageal wall. In addition, the stent braiding has a variable gradient, intended to comply better...
with peristalsis, similar to knitted enteral stents. Stents, which incorporate struts or other mechanical retention mechanisms should be considered with care. While these may perform really well in strictures at the gastro-esophageal junction, the anchoring structures may engage in the fistula, potentially increasing the size of the defect. Stent fixation with endoscopic clips or additional sutures has been described, but a naturally migration-resistant stent would be preferable.

**Altered anatomy**

With improving surgical techniques and better outcome after neo-adjuvant chemotherapy, increasing numbers of patients undergo radical surgery. Inevitably there are more patients who develop subsequent tumor recurrence. The altered anatomy, however, may have completely different requirements for stent fixation and conformability than a native esophagus and standard stents may no longer be the best choice.

**Method of Stent Placement**

Esophageal stents can be placed endoscopically or radiologically and the techniques are well established. Recent international consensus guidelines have recommended a combined endoscopic and fluoroscopic approach for placement of the colonic stents and the value of the endoscope is beyond question for duodenal stenting. However, it is important to understand that the benefit of using an endoscope lies primarily in straightening out tortuous anatomy and providing an overtube for a catheter and guide wire rather than in the ability of identifying the stricture visually. A tortuous colon is difficult to negotiate with catheter and wire and a stomach dilated from gastric outlet obstruction provides such a capacious space that catheter and guide wire alone loop in the stomach and may be impossible to advance into the duodenum. In the esophagus, however, access to the stricture is through a short, straight route and non-endoscopic technique using a 5F to 6F (1.7–2 mm) catheter is less traumatic, cheaper and usually quicker. Most esophageal stent delivery systems currently exceed the working channels of therapeutic gastroscopes and thus the stents need to be placed alongside the scope after placement of the guide wire. This negates the benefit of through-the-scope technique of enteric stent systems. If endoscopic guidance is used only, the scope must be passed through the stricture to assess the tumor and the anatomy beyond it. This may require pre-dilatation, which carries the risk of perforation or a lack of certainty of correct guide wire placement. Unless fluoroscopy is used as well, the position of the guide wire and the distal end of the stent cannot be controlled and deployment of the stent cannot be monitored in real-time.

Sadly, the collaboration between interventional endoscopists and interventional radiologists is threatened by competitive interests, notably in healthcare systems where remuneration is by procedure. This prevents good cooperation between the specialties and provision of the best possible service to the patient.

**Stent Choice**

An amazingly large number of different stent designs are available for the esophagus, reflecting the fact that there is no clear understanding what properties make the ideal stent. The overwhelming majority is constructed from braiding a nitinol wire into a tubular structure with flared or “dog bone” shaped ends to achieve fixation by mechanical friction. At present the commonest configuration is a fully covered stent to prevent tumor ingrowth and with a capture string to allow stent removal, if needed.

While stainless steel is an easier material to manufacture stents from and has superior bio-resistance and radiopacity, nickel titanium alloy (nitinol) is very much the material of the moment due to its super-elasticity and inherent shape memory. These properties and the resultant possibilities for stent design have been described in detail.

The option to remove a stent is increasingly important. Improved palliative chemo- and radiotherapy is extending patient survival as well as potentially shrinking the esophageal tumor, which increases the risk of stent displacement. Stent migration rates in the mid-esophagus are in the region of 5%, while migration rates of stents placed with the lower end at the stomach average 15% to 20% with some designs performing markedly worse than others. The risk of migration is increased with subsequent chemo- or radiotherapy.

In our personal experience, the most migration resistant stents are those with either a mechanical anchor, which will arrest stent movement at the top end of the stricture or stents that can absorb peristalsis through their particular construction of the stent skeleton. This type of “knitted” construction also allows stent to be removed by inverting them through themselves. Capturing the removal string at the distal end allows the stent to be peeled away from the esophageal wall thus avoiding the trauma of extracting the stent through the stricture. Stent removal can be facilitated by cooling the stents by injection of iced water. Although an awkward maneuver, this dramatically reduces their rigidity, essentially rendering them a fairly floppy structure.

The covering membrane in most stents is applied by dip-

---

**Fig. 4.** (A) Examples of stents with partially covered ends (left to right): Wallflex esophageal (Boston Scientific); Evolution esophageal (Cook, Letchworth, UK); Ultraflex esophageal (Boston Scientific); EGIS colonic double covered (S&G Biotech, Seongnam, Korea). (B) Oversized 25 mm Danis Seal stent with variable braiding (Ella-CS, Hradec Králové, Czech Republic).
ping the stent in silicon. This fixes the wires against each other, increasing the rigidity of the stent skeleton and reducing the ability to conform around anatomical bends, such as the gastro-esophageal junction. Where covering membranes are applied to the outside of the stent skeleton, the conformability is preserved resulting in much better alignment with curvaceous anatomy and an improved lumen around the apex of the flexure.

Much emphasis has been placed in the past on the radial expansion force of a stent, but no figures exist on the ideal radial force and there is significant variation among existing designs. A rigid stent is more likely to be propelled by peristalsis, while a stent, which is able to absorb compressive forces, is more likely to stay in place.

Case Reports

Stent fracture

A 57-year-old man with metastatic esophageal carcinoma had a Hanaro stent (MI Tech, Pyeongtaek, Korea) inserted for grade 3 dysphagia.

Three weeks later at the baseline CT for chemotherapy the stent was seen to have migrated completely into the stomach. The patient continued to manage a semisolid diet throughout chemotherapy, but follow-up scans showed increasing disintegration of the stent with the distal 1/3 sheared off and passed per viae naturales after 7 months (Fig. 5A).

Eight months after the original stent, dysphagia progressed and a 20 × 110 mm valved EGIS stent (S&G Biotech, Seongnam, Korea) was inserted (Fig. 5B). This caused persistent retrosternal pain, but dysphagia improved from grade 3 to 1. Twelve months after initial stent insertion he was managing most solid foods, he had a performance status of 1 and stable disease on CT.

Cervical esophagus

A 77-year-old lady with a T4N1M0 squamous cell carcinoma of the upper esophagus was referred for esophageal stent insertion for complete dysphagia. A previous radiologic gastrostomy had required ultrasound-guided puncture of the stomach to place a Chiba needle for inflation. The tightness of the stricture had precluded passing an inflation catheter from the mouth. She had a tracheal stent placed previously due to tumor infiltration and was undergoing palliative chemotherapy. Radiotherapy had been discounted because of the risk of a tracheo-esophageal fistula.

An 18 mm diameter EGIS stent (S&G Biotech) was placed antegrade with the top in the dilated segment above the stricture just below cricopharyngeus, but shortened/migrated with the top below the stricture (Fig. 6A).

A second attempt at stent insertion was made, but this time it was not possible to pass a guidewire through the stricture. The 12F balloon gastrostomy was removed and the stent passed from below with a 6F/65 cm KA2 catheter (Merit Medical, Coatbridge, UK). The esophageal stent delivery system was inserted from below through the gastrostomy (Fig. 6B) and the distal end of the stent deployed within the hypo-pharynx, allowing stent shortening to take place (Fig. 6C). The part-deployed system was withdrawn into the esophagus until the upper head was correctly positioned in the cervical esophagus below CPS (Fig. 6D, 6E). At that point the rest of the stent was deployed.

Following stent insertion the patient was able to manage a semi-solid diet and gained 1 kg in weight. The patient died 5 months later not requiring further intervention.

Esophageal fistula without stricture

A 71-year-old man was undergoing treatment for metastatic adenocarcinoma of the left lung. Besides extensive nodal disease a CT scan showed tumor tissue encasing the left main bronchus and infiltrating the mid-esophagus (Fig. 7A). Following radiotherapy the patient developed a tracheo-esophageal fistula into the left main bronchus (Fig. 7B) and was referred for esophageal stent insertion. The patient was aware of the poor prognosis, and requested all effort be made to allow him to enjoy three bottles of his favorite Italian beer he had waiting in his fridge.

The patient attended with a nasogastric tube in situ. Under conscious sedation this was removed over a guidewire and after outlining of the fistula a 24 × 100 mm double-covered EGIS colonic stent (S&G Biotech) was placed via the nose and a naso-jejunal feeding tube reinserted at the end of the procedure over the
same guide wire (Fig. 7C–7E). A contrast swallow the following
day showed a well expanded stent with no evidence of bypassing
or extravasation and was discharged home.

Although the patient’s request regarding the artisan beer could
be accommodated, he subsequently developed aspiration due to
impaired airway closure, possibly as a para-neoplastic phenome-
on. He developed worsening dysphagia due to recurrence at the
esophago-jejunostomy (Fig. 8A). A Niti-S single stent (Taewoong
Medical, Gimpo, Korea) was placed in the local hospital in Janu-
ary 2014. Following this the patient had complete aphagia and
unrelenting chest pain. A CT scan showed the stent impacted with
the lower end in the angled run-off of the jejunum and the top
just below the upper margin of the stricture (Fig. 8B). The patient
was referred to our hospital for further management.

Endoscopy was performed in February 2014 by the radiolo-
gists through a Guardus overtube (US Endoscopy, Mentor, OH,
USA). This confirmed the proximal end of the stent to be impacted

Altered anatomy

A patient with a gastric carcinoma had a total gastrectomy
with positive resection margins in 2012 followed by chemother-
apy. He developed worsening dysphagia due to recurrence at the
esophago-jejunostomy (Fig. 8A). A Niti-S single stent (Taewoong
Medical, Gimpo, Korea) was placed in the local hospital in Janu-
ary 2014. Following this the patient had complete aphagia and
unrelenting chest pain. A CT scan showed the stent impacted with
the lower end in the angled run-off of the jejunum and the top
just below the upper margin of the stricture (Fig. 8B). The patient
was referred to our hospital for further management.

Endoscopy was performed in February 2014 by the radiolo-
gists through a Guardus overtube (US Endoscopy, Mentor, OH,
USA). This confirmed the proximal end of the stent to be impacted

Fig. 6. (A) Contrast injection during stent insertion: The top markers of the initial EGIS esophageal stent (S&G Biotech; white arrowheads) are seen below the stric-
ture. The top of the stricture is at C7 [black arrow], one vertebral body below the impression of cricopharyngeus (CPS; black arrowhead). White arrow, Ultraflex tra-
cheal stent [Boston Scientific, St. Albans, UK]. (B) The tip of the delivery system (arrow) has been advanced retrogradely through the gastrostomy past the upper end
of the first stent (arrowheads) into the oropharynx. (C) The distal end of the stent has been released in the pharynx. Black arrowheads, stent markers; black arrow,
ing marker on the constraining sheath at the level of CPS. A 6F catheter has been inserted from the mouth to allow outlining of the anatomy with contrast (white
arrowhead). (D) The part-deployed is withdrawn until the distal markers (arrowheads) lie at C7. Arrow, ring marker on constraining sheath. (E) Final result: Limited
initial expansion across the stricture at the top of the tracheal stent (arrowheads), but with a good flare of the stent head above it.

Fig. 7. (A) Axial computed tomography shows tumor involving the esophagus and the left main bronchus (arrow). There is left hilar adenopathy and collapse of
the left lower lobe (arrowhead). (B) Contrast swallow shows a large fistula into the left main bronchus (arrow). (C) Stent insertion (patient prone): Contrast injection
through a per-nasal catheter (arrowhead) demonstrates the fistula (arrow). (D) Advance of 10F colonic delivery system through the nose following the access pro-
vided by the naso-gastric tube. (E) Deployed 24 mm colonic stent (arrowheads). The paperclip on the patient indicates the level of the fistula.
under a shelf of tumor. The removal suture could be grasped with
endoscopic forceps and the upper stent head dis-impacted by ad-
vancing the endoscope while applying traction to the purse string
(Fig. 8C, 8D). Following removal, the esophageal lumen was wide
enough to pass the endoscope, suggesting little residual stricturing
at that point. The patient could manage most solid food the same
day and further intervention was deferred.

Over the next 3 months, disease progressed and dysphagia
slowly worsened. In May 2014, a 24 × 100 mm double covered
EGIS colonic stent (S&G Biotech) was deployed easily around the
acute angle of the anastomosis (Fig. 9). Initial expansion, even
after 5 minutes, was poor and limited balloon dilatation to 12 mm
was performed with a good radiological result and the patient
managing a semisolid diet including the occasional pie.

A CT scan 4 months later showed tissue ingrowth into the
proximal uncovered segment of the stent, as well as fracture of
some wire struts and separation of the two layers of the nitinol
skeleton (Fig. 10). This was associated with recurrence of symp-
toms and two further 24 × 100 mm double-covered EGIS colonic
stent were placed radiologically, also covering additional stricture
formation at the distal end. The patient resumed most normal
activities and regained 3 kg in weight. Tumor overgrowth at the
proximal end in July 2015 necessitated insertion of a further
standard esophageal EGIS stent. Notably 3 years after the original
surgery and 12 months after the initial stent insertion for pallia-
tion of recurrent tumor the patient was well with a performance
status of 1, but died 2 months later from metastatic disease.

Discussion

Survival of cancer patients, even with metastatic disease
is ever improving. As a consequence patients are increasingly
outliving their stents with more re-interventions being required,
either due to stent obstruction from tumor growth or because the
stent has perished. Early stent failures can often be identified on
conventional staging CT, but it usually requires the additional
curiosity of an interventional radiologist to identify the subtle
abnormalities. All CT findings demonstrated were missed by the
reporting diagnostic radiologist.

With the development of surgical techniques and improved
down-staging from neo-adjuvant chemotherapy more patients will have radical surgery and consequent non-standard anatomy. This may require unconventional access routes or a joint approach between radiologists and endoscopists. Different stent systems have different properties and need to be chosen to match the respective context. Braided stents tend to have a higher radial force but also a higher longitudinal rigidity, compared with knitted stents. Stent shortening as a function of their expansion, as well as stent shape can be critical if the target zone is not of a standard configuration. This requires familiarity with a variety of different stent designs and their delivery systems, even if they were intended for application in another organ. Good collaboration across different specialties and between interventionists and industry is essential in order to give patients the best possible outcome.

Devices and their materials need to be improved to ensure good long-term performance. Nitinol has become the alloy of choice due to its superelastic nature and shape memory properties, but may not have sufficient bio-resistance in a chemically hostile environment. As palliative treatment improves and patient survival increases, the options of temporary stenting and brachytherapy may need to be considered as alternatives for treating esophageal obstruction. Similar to the “bridge-to-surgery” concept in colonic cancer, “bridge-to-chemo/radiotherapy” with biodegradable or temporary metal stent insertion might prove a better strategy and increase long-term options.

More and more patients return for re-intervention and the increasingly important question is “What am I going to do ‘next’ time?”

Conflicts of Interest

DWE has acted as technical consultant for S&G Biotech. HUL has acted as technical consultant for Ella-CS and S&G Biotech.

References

1. British Society of Interventional Radiology. ROST-Registry of Oesophageal Stent- ing: first report 2004. Henley-on-Thames: Dendrite Clinical Systems; 2004.
2. Rana SS, Bhasin DK, Sidhu GS, Rawal P, Nagi B, Singh K. Esophageal nitinol stent dysfunction because of fracture and collapse. Endoscopy. 2009;41 Suppl 2:E170-1.
3. Khara HS, Diehl DL, Gross SA. Esophageal stent fracture: case report and review of the literature. World J Gastroenterol. 2014;20:2715-20.
4. Chhetri SK, Selinger CP, Greer S. Fracture of an esophageal stent: a rare but significant complication. Endoscopy. 2008;40 Suppl 2:E199.
5. Conio M, Bianchi S, Filiberti R, Rapiè A, Barbieri M, Bilardi C, et al. A modified self-expanding NiTi-S stent for the management of benign hypopharyngeal strictures. Gastroshter Endosc. 2007;59:14-20.
6. Pavlov PV, Sokolov VV, Pirogov SS, Karpova ES, Pogorelov NN, Sukhin DG. Endoscopic stenting of malignant stenosis in the cervical esophagus. Eksp Klin Gastroenterol. 2014;4(3):67-71.
7. Shin JH, Song HY, Ko GY, Lim JO, Yoon HK, Sung KB. Esophagorespiratory fistula: long-term results of palliative treatment with covered expandable metallic stents in 61 patients. Radiology. 2004;232:252-9.
8. Kim JH, Shin JH, Song HY, Choi CM, Shin TS. Esophagorespiratory fistula without stent: case report and literature review. J Vasc Inter Radiol. 2011;22:84-8.
9. Siriam PV, Das G, Rao GV, Reddy DN. Another novel use of endoscopic clipping: to anchor an esophageal endoprosthesis. Endoscopy. 2001;33:724-6.
10. Silva RA, Dinis-Ribeiro M, Brandão C, Mesquita N, Fernandes N, Lomba-Viana H, et al. Should we consider endoscopic clipping for prevention of esophageal stent migration? Endoscopy. 2004;36:369-70; author reply 370.
11. Rieder E, Dunn CM, Martinez IV, Casero MA, Swanstrom LL. Endoscopic suture fixation of gastrointestinal stents: proof of biomechanical principles and early clinical experience. Endoscopy. 2012;44:1121-6.
12. Kantsevoy SV, Bitner M. Esophageal stent fixation with endoscopic suturing device (with video). Gastrointest Endosc. 2012;76:1251-5.
13. Fujii LL, Bonin EA, Baron TH, Gostout CJ, Wong Kee Song LM. Utility of an endoscopic suturing system for prevention of covered luminal stent migration in the upper GI tract. Gastrointest Endosc. 2013;71:787-93.
14. Lausch HH, Martin DF, Do YS, Köcher M, Valette PJ. Interventional radiology for the management of inoperable carcinoma of the oesophagus. Endoscopy. 2003;35:1049-57, discussion 1058.
15. Ross AS, Kozarek RA. Esophageal stents: indications and placement techniques. In: Kozarek R, Baron T, Song HY, editors. Self-expandable stents in the gastrointestinal tract. New York: Springer; 2013, p. 129-40.
16. van Hooff JE, van Halsema EE, Vanhierivelt G, Beets-Tang RG, DeWitt JM, Donnelly F, et al; European Society of Gastrointestinal Endoscopy. Endoscopic stenting of malignant stenosis: experience in 70 patients. Endoscopy. 2003;35:1049-57, discussion 1058.
17. van Hooff JE, van Halsema EE, Vanhierivelt G, Beets-Tang RG, DeWitt JM, Donnelly F, et al; European Society of Gastrointestinal Endoscopy (ESGE). Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2014;46:990-1053.
18. van Hooff JE, van Halsema EE, Vanhierivelt G, Beets-Tang RG, DeWitt JM, Donnel- lain F, et al; European Society of Gastrointestinal Endoscopy (ESGE). Self-expand- able metal stents for the management of inoperable carcinoma of the oesophagus. Endoscopy. 2003;35:1049-57, discussion 1058.
19. Ko HK, Song HY, Shin JH, Lee GH, Jung HY, Park SI. Fate of migrated esopha- geal and gastroduodenal stents: experience in 70 patients. J Vasc Inter Radiol. 2007;18:725-32.
20. Schoppmann SF, Langer FB, Prager G, Zacherl J. Outcome and complications of long-term self-expanding esophageal stenting. Dis Esophagus. 2013;26:154-58.
21. Martins BC, Petes FA, Medrado BF, de Lima MS, Pennacchi CM, Kagawati PS, et al. Endoscopic management and prevention of migrated esophageal stents. World J Gastroint Endosc. 2014;6:49-54.
22. Suntharanathan J, Edwards DW, Mullan D, Martin DF, Lausch HH. New “knitted” EGIS esophageal stent allowsatraumatic inside-out removal by inversion. Endoscopy. 2013;45 Suppl 2 UCTN=E187-8.
23. Merkel D, Brinkmann E, Wiens D, Derwahl KM. In situ cooling with ice water for the easier removal of self-expanding nitinol stents. Endosc Int Open. 2015;3:E51-5.
24. Hirdes MM, Vlieggar F, de Beule M, Siersena FD. In vitro evaluation of the ra- dial and axial force of self-expanding esophageal stents. Endoscopy. 2013;45:997-1005.