Editorial

Blitzkrieg for Barrett's Esophagus Containing Early Neoplasia

"You hit somebody with your fist and not with your fingers spread"

— Heinz Wilhelm Guderian (German WWII general and tank commander, 1888–1954)

Blitzkrieg (German, "lightning war") describes a military doctrine in which a special force concentrates its attack on a small section of the enemy front, and then, once the latter is broken, it proceeds with a broader attack by a fully motorized and mechanized army to pose deep thrusts into the opponent's defenses in order to achieve a rapid and decisive victory. A since famous military tactic, *Blitzkrieg* was successfully implemented by the German general Heinz Guderian in the early phases of World War II, during the Polish and Russian campaigns. The German armed forces referred to a *Schwerpunkt* (focal point) in the planning of operations; it was the point where maximum military force was exerted, in an attempt to seek a decisive outcome to the battle.

As an analogous clinical situation, "endoscopic" blitzkrieg, the multicenter European effort by Pouw, et al, described in the current issue of *Clinical Gastroenterology and Hepatology*,[1] sought to assess the safety and efficacy of radiofrequency ablation (RFA) in conjunction with baseline endoscopic resection (ER) for high grade intraepithelial neoplasia (HGIN) and early cancer (EC) in patients with Barrett's esophagus (BE). The authors used ER and RFA to eradicate not only the neoplasia manifested as a visible lesion(s) (the *Schwerpunkt*) but also—and very importantly—the accompanying field of residual neoplasia and metaplasia in all cases. In this way, the most active and biologically dangerous areas of HGIN and EC were resected and histologically assessed *en bloc*, while the remaining areas of enemy soil (aka, metaplasia) carrying the potential of future assault on the patient were then carpet-bombed into oblivion. More plainly stated, visible (nodular or irregular) early neoplastic lesions were endoscopically resected, followed by serial (circumferential or focal) RFA sessions until complete eradication of visible Barrett's tissue was achieved (reported by the authors as a complete histological response for IM (CR-IM)).

Pouw et al[1] report on a prospective cohort trial that was conducted at 3 tertiary care European medical centers and involved patients with BE (maximum length 12 cm), aged 18–85 years, who had HGIN or EC on 2 endoscopies during the preceding 6 months and had no signs of local or distant metastasis on endoscopic ultrasonography or computerized tomography scan. Patients were excluded if they had esophageal adenocarcinoma at the vertical resection margin, >T1*sm1* invasion, poor differentiation, or angiolymphatic invasion, esophageal stenosis preventing passage of a 11.3 mm endoscope, persistent visible lesions after ER and pre-RFA, or invasive cancer on biopsies after ER and pre-RFA. In order to qualify, patients underwent 2 high resolution endoscopies with documentation of the BE landmarks using the Prague classification system. Visible lesions were removed with ER followed by 2 additional endoscopies with 4-quadrant, 1 cm biopsies to exclude residual cancer and residual nonflat lesions.

All procedures were performed on an outpatient basis and all patients were treated with high dose proton pump inhibitor therapy (esomeprazole 40 mg twice a day) during the entire study period together with sucralfate suspension and ranitidine 300 mg for 2 weeks after endoscopy. ER of any nonflat lesions was discretionally performed using the ER cap technique, the multiband mucosectomy (MBM) technique, or endoscopic submucosal dissection. For circumferential RFA, the HALO^{360} ablation catheter of appropriate outer diameter was introduced and energy delivered (12 J/cm^2, 40 W/cm^2) to the entire BE segment. For secondary focal ablation, each island or tongue of residual metaplasia was treated with the HALO^{90} catheter (15 J/cm^2, 40 W/cm^2). In all patients, the gastroesophageal junction was treated circumferentially with the HALO^{90} catheter during at least 1 treatment session (2 × 2, 15 J/cm^2) to ensure metaplasia clearance.

It is notable that fully 2 thirds of the study patients had EC as their baseline diagnosis, with the remainder having HGIN. After baseline ER and prior to RFA, about 40% of the patients had residual HGIN, while the remainder had residual LGIN or nondysplastic IM. The study's primary outcome, complete eradication of all residual neoplasia after ER, was achieved in 21 of 21 patients (CR neoplasia, 100%), while complete eradication of all residual IM after ER (CR-IM) was achieved in 23 of 24 patients (CR-IM 96%). Both outcomes were meticulously assessed during endoscopy with 4-quadrant biopsies every 1 cm of the original Barrett's segment 2 months after the last therapeutic intervention. It is important to re-emphasize that the investigators used RFA after baseline ER to eradicate all residual BE, not just residual neoplasia.

As with any battle, there were some complications: 1 esophageal perforation occurred after baseline ER by the cap technique and it was treated nonsurgically with clips and a covered stent. There were also 2 RFA complications: 1 patient presented with melena 2 weeks after focal ablation and 2 visible vessels in the ablated area were preventatively clipped. A second patient had a wide field baseline ER and then developed a stenosis after the first RFA procedure, which resolved after 5 endoscopic dilations. The authors note that this stenosis would likely not have occurred in the absence of prior ER. There was no mortality or long term morbidity.

As with any successful military campaign, intelligence (strategic, operational, and tactical) is essential. In this endoscopic campaign, Pouw et al[1] effectively used all available intelligence in the era of modern diagnostic and therapeutic endoscopy. Their subjects were patients who had been identified previously as having BE in the context of endoscopic screening (strategic intelligence); the metaplasia and/or early neoplasia were thoroughly evaluated by 2 high resolution endoscopies, endoscopic ultrasonography, and computerized tomography, as well as expert histopathology of large tissue samples in order to secure deep and lateral margins (operational intelligence); and the tissue removal and destruction, followed by the repair and re-epithelialization over time, was accomplished methodically by using ER or RFA and high resolution endoscopy until their campaign's end, that is, the complete normalization of the esophageal mucosa (tactical intelligence). It is clear that this is the manner in which BE should be managed in 2009 if we are

to ever claim victory against esophageal adenocarcinoma (an entirely preventable disease, in my humble opinion), while sparing our patients an esophagectomy with its morbidity, mortality, and associated quality of life aftermaths.

Perhaps the most important outcome of this study is that Pouw et al terminally defeated the enemy and there was no counter attack. Fully 2 thirds of the patients had intramucosal carcinoma or invasive cancer (*sm*1) at baseline, and no cancer persisted or progressed. For those patients with residual HGIN after ER, we would expect 10%–20% to progress to invasive cancer without further intervention. Instead, RFA after ER resulted in ***zero*** progression in this group. These impressive outcomes comport with those of several other well designed prospective cohort trials and 2 randomized controlled trials, all demonstrating very high rates of complete eradication of metaplasia and related neoplasia as well as decreased disease progression.[2–11] The evidence is now clear and we should put this debate to rest, that is, ER and RFA change the natural history of neoplastic BE in a substantial way by completely eradicating the metaplastic/neoplastic epithelium, and eliminating progression to higher grades of intraepithelial neoplasia and invasive cancer.

There are number of additional key messages from this trial. Performing RFA is safe after ER, even in up to 12 cm BE segments, as long as one abides by some important tenets, such as avoiding wide field ER, allowing time for intermediary healing, and limiting resection to a staging procedure. The flow diagram of the trial and the rigor with which these patients were vetted, involving multiple endoscopies, pathology confirmation, restaging, and detailed mucosal assessment are exemplary. Although the number of RFA sessions was higher in this study than what is seen in routine BE care today, this could be due to the learning curve still in place with RFA technology when they started enrolling patients in 2005. The authors included the cardia in their outcomes and although probably not necessary, it is reassuring to know that this region was CR in all patients as well. This finding refutes the hypothesis set forth by some that the cardia is somehow altered after ablative therapy, placing it at higher risk to harbor neoplasia.[12] Perhaps this potential risk is associated with *incomplete* (ineffective) ablative therapies, in contradistinction to the strategy presented by Pouw et al.[1]

To date, the recommended management strategies for BE with low grade intraepithelial neoplasia and nondysplastic metaplasia are confined exclusively to surveillance endoscopy for the life of the patient with the goal to detect neoplastic progression.[13] The recommendation to survey, rather that proactively eradicate the abnormal tissue may be predicated on suboptimal safety and efficacy profiles of previously studied therapeutic modalities, such as wide field EMR, APC, MPEC, laser, PDT, and others. Applying any of these therapies to LGIN or metaplasia has not made sense from a risk-benefit standpoint and therefore guidelines have not suggested earlier intervention. Does RFA with or without ER change this equation? What level of safety and efficacy do we need in order to recommend early preventive intervention in BE? How much follow-up with durability do we need to justify use of RFA for nondysplastic BE? Do we need cancer endpoints, mortality, or just very high CR rates as we have? These are all key questions in making a decision to ***actively*** intervene early in LGIN and nondysplastic patients, or ***passively*** survey and wait for the neoplastic progression to occur, as current guidelines recommend.

The Case for Early Intervention in LGIN and Nondysplastic Disease

As stated earlier, there are a number of well designed cohort studies, several registries, and 2 randomized controlled trials that provide ample evidence that RFA is safe, effective, and durable for completely removing the metaplastic and neoplastic epithelium. We know from recent published studies that LGIN, when confirmed by at least 2 expert pathologists, has a similar risk for neoplastic progression as HGIN, a disease state that we proactively treat now.[14,15] Further, LGIN is "neoplasia," and the march toward cancer has begun. By comparison, the estimated lifetime risk for a patient with nondysplastic BE to progress to esophageal adenocarcinoma is 5%–8%, admittedly lower than that of LGIN and HGIN, but not dissimilar from the lifetime risk of a patient with colonic polyps (all comers) to progress to colorectal cancer.[16,17] Metaplasia and LGIN are at the beginning of the sequence of disease progression histologically, but many of the epithelial clones have accumulated genetic alterations that cannot be observed on microscopy. These genotypic alterations occur well in advance of the phenotypic alterations (histology) that they ultimately precipitate. These earlier lesions (LGIN and metaplasia) also tend to be flat, and occur in patients earlier in the gastroesophageal reflux disease evolution, with typically less severe reflux, better esophageal function, and higher likelihood for successful eradication. From an economic perspective, 2 recent cost-utility studies have indicated that RFA is the preferred strategy, over surveillance and other interventions, for LGIN and metaplasia.[18,19] These many issues coupled with the well recognized risk of biopsy sampling error (missing areas of more advanced disease such as HGIN and early cancer), interobserver variation for ascertaining the correct histological diagnosis, patient compliance with lifetime surveillance, and BE-associated impact on patient quality of life, LGIN and nondysplastic metaplasia are logical actionable entities, warranting intervention. Beyond reducing the incidence of neoplastic progression, consider the impact of successful eradication on future surveillance requirements. A conservative example, a patient with LGIN who undergoes RFA and achieves CR for neoplasia but has residual IM only, their surveillance interval is cut from every 6 months to every 36 months, a 6 fold reduction in services.

In summary, Pouw et al[1] are to be congratulated on executing a superb study of combined modality ER and RFA for patients with BE containing neoplasia. Their results, corroborated by many other studies, confirm that this approach represents the state-of-the-art in 2009. But let's not stop there. If we are to avert the occurrence of a deadly, and arguably *preventable* cancer (esophageal adenocarcinoma), we must intervene earlier in the metaplasia-neoplasia-invasive cancer sequence and take a more proactive step by eradicating LGIN and metaplasia prior to the development of advanced neoplasia and invasive cancer. That is the setting where any modality (ablation, resection, chemoprevention) will work the best. As Heinz Guderian said, "Nicht kleckern, klotzen!" (Don't fiddle, smash!).

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