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Research Article

Evaluation of Direct and Frontal Tissue Acquisition Technologyas Prerequisite for Molecular Profiling of Cancer

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Abstract

Personalized medicine, the selection of both patient and treatment, is based on a multitude of 'in-vitro' pathology and molecular biology analyses that are almost exclusively performed on sliced and homogenized diseased tissues. Appropriate technologies are crucial to comply with increasingly demanding clinical needs. The direct and frontal (D&F) biopsy technology, used under the most modern imaging guidance, is evaluated for this purpose. 1209 biopsies in 909 patients were evaluated in two clinical centers for various organs with regard to efficacy, comfort and safety in about 97% of the patients assessed with the D&F technology, surgery can be avoided without loss of diagnostic accuracy. Samples up to 300 mg and with average diameter of 3.81 mm are consistently harvested for various organs. The tools are easy to use, well tolerated, and relatively low in cost. It is concluded that optimal personalized diagnostics and treatments are available now for almost every cancer patient in every stage of the disease without surgery.

INTRODUCTION

There is reasonable hope that biomolecular classification of cancers before any systemic treatment may increase response rates, prolong progression-free survival and improve overall survival, creating a more favorable balance between treatment efficacy and side effects [1,2]. Numerous biomolecular platforms are available now and with the advances in high-performance output and next-generation sequencing, up to hundreds of tests can be offered for specified cancers [3].

In contrast to histology, histochemistry, and immunohistochemistry, where most cancer cells can be visualized in an environment of normal or contaminating tissue or even blood, most biomolecular platforms use tissue homogenates. One of the main concerns for all biomolecular tests is pre analytical tissue quality [4,5]. Multiple small specimens suffer from the presence of a number of samples wherein no cancer cells are present. In addition, they contain more blood, caused by repeat sampling, making RNA-based tests rather unreliable [6]. Therefore, specimens should be appropriately sized to guarantee material for all tests needed [7,8], meaning quantities up to 100 mg [9,10]. Finally, the material should be representative of the entire disease, requiring imaging guidance to ensure that the lesion of interest appears in great proportions in the biopsy specimen [11,12].

While tissue quality is most important for proper treatment and patient selection [13], safety and comfort are other vital characteristics of a biopsy procedure. Newer technologies may indeed help in overcoming fear for complications during tissue sampling, for example in head & neck cancers and thoracic diseases, leading to increased applications for transdermal approaches. Similarly, safe and reliable techniques may lower the threshold for repeated sampling in cases of relapsing disease.

Current instruments such as forceps, aspiration cytology (fine needle aspiration cytology – FNAC), tru-cut (core needle biopsy – CNB) and vacuum assisted tools (VABs) present major limitations. With the forceps, the trauma on the mucosa is often severe in comparison to the sample harvested; FNAC lacks any histological assessment [14] and is limited by an unacceptable percentage of false negative findings. CNBs harvest tissues up to 20 mg only [15] and the shooting characteristics of tru-cut biopsy

guns make them unsuitable for vascularized deeper tissues or in the presence of delicate structures such as large blood vessels, nerves and bones. VABs create local blood, lack accuracy and are only acceptable for some indications in predominantly fatty peripheral tissues with less vascularization such as the breast.

The novel direct and frontal (D&F) macrobiopsy has been proposed as an attractive alternative to diagnostic surgery allowing delivering high quality, samples with maximal comfort for the patient in almost every organ of the body. The direct approach refers to the needle tip simply going into and through the lesion. In contrast to tru-cut or VABs systems, the direct approach avoids any shot once the device is positioned in front of the target. The frontal aspect refers to the tissue being taken from the most distal end of the needle, instead of a more lateral approach to the lesion. Moreover, a frontal approach facilitates a full core acquisition, i.e. maximizing the core diameter in relation to the needle size.

The present paper describes the evaluation of a D&F system with regard to efficacy, comfort and safety as well as prerequisite to advanced diagnostics in comparison to surgery and/or clinical follow-up in a patient population of two large hospital clusters in Belgium.

MATERIALS AND METHODS

Between January 2005 and February 2014, all patients presenting with suspicious tumor lesions to the department of oncology (Ziekenhuis Oost-Limburg, Genk; Jessa Ziekenhuis, Hasselt; and H. Hartziekenhuis, Tienen) and the department of medical imaging (CHU de Charleroi, HôpitalA.Vésale, Monitigny-le-Tilleul) were consecutively included in the study (n=909). Patients, all Caucasians, provided informed consent for the biopsy procedure, as well as for participation to the registry, according to the requirements of the local institutional ethical board. Only patients with bleeding disorders were excluded from participation.

The biopsy procedure was standard and has been described elsewhere [16]. In brief, all patients underwent clinical investigation and diagnostic imaging (mainly ultrasound (US), Computerized Tomography (CT), Magnetic Resonance Imaging (MRI) and/or Positron Emission Tomography (PET-CT)). A multi-disciplinary discussion among oncologists, pathologists and radiologists completed the work-up. Any lesion, ranging from one millimeter (e.g. micro calcification) to a centimeters large lesion that could be visualized was considered for biopsy.

The patient was subsequently installed in a comfortable position. The type of imaging guidance was chosen depending on the best technique to visualize the lesion. In general, ultrasound was preferred for superficial subdermal lesions, while CT or MRI was generally used for transdermal lesions deeper than 5 cm. For skin and gynecological application biopsies were taken under direct vision or with colposcopy. All interventions were made by one of the authors. The biopsy entry site was cleaned and disinfected. A surgical draping was applied to prevent infection and to allow a clean working area, anticipating potential dermal blood absorption. Lidocaine with 1% adrenaline was injected with attention to the most painful areas (skin, periost etc.). The whole biopsy tract was anesthetized up to a maximum volume of 20 ml (usually less than 10 ml). The entrance in the skin was cross incised to prevent scar formation and to facilitate both penetration and rotational movements of the biopsy tool. The Spirotome single use kit (MedInvents, Belgium; Cook Medical, USA) consisting of a trocar, cutting cannula, receiving needle and release element was then used (Figure 1). Available needle diameters ranged from 8 to 10 Gauge for compressible target sites (e.g. skin, head & neck region, superficial lymph nodes etc.), while 10 to 14 Gauge needles were preferred for deeper lesions where compression is not possible (e.g. lungs, abdominal organs etc.), or for patients taking oral anticoagulants or with incapacitating performance index. In general, we aimed to use the largest needle (8 Gauge) to ensure enough material in the specimen. Similarly, different lengths were available ranging from 6 to 35 cm depending on the type of intervention anticipated.

For transdermal applications, the trocar (T in Figure 1) with cutting cannula (C) typically moves forward with a pushing and twisting movement up to the target lesion under imaging guidance. Once the cutting cannula is in front of the lesion, the trocar is removed and the receiving needle with helix inserted. By clockwise rotation, the helix goes then through the target lesion. Once the desired distance across the lesion is covered, the cutting cannula is equally rotated in a clockwise direction over the helix. The marks on the receiving needle (R1 through R5 in Figure 1) provide information about the distance crossed. With the knob of the cutting cannula at marker R1, the helix still is in the cutting cannula. Each additional 5 mm penetration is then marked, with R5signaling full penetration (20 mm) of the helix. The external end of the receiving needle contains a plastic knob with a vacuum valve in it. This vacuum may be important in order to achieve fluid or very soft samples (e.g. liver, myxoid or necrotic tissues). In these cases a syringe is mounted on the luer lock and vacuum is applied. The syringe can be removed when needed, and a valve allows retaining the vacuum for some minutes. When the sample has been cut, the receiving needle can be removed and the biopsy specimen freed on the release element. A second biopsy

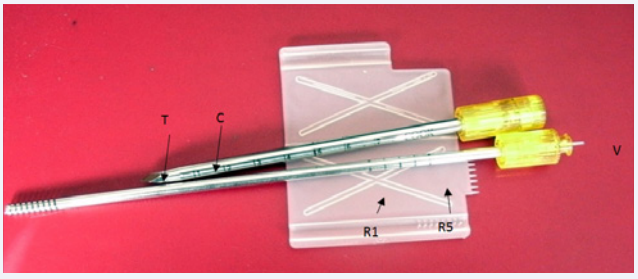

Figure 1 Typical Spirotome Set. The Spirotome kit contains a Trocar –T- and Cutting Cannula –C- and the receiving needle with helix. In this figure the trocar is already mounted in the cutting cannula. The cutting cannula has one centimeter marks to facilitate guidance. The receiving needle has 5 marks (R1 to R5) on the proximal end to guide the penetration of the helix. R1 being the start and end position and R5 maximal exposure of the helix before cutting. Both cutting cannula and receiving needle have a luer lock on the proximal end to accommodate a syringe for aspiration. The valve (V) in the plastic knob of the receiving needle can be used to apply vacuum that is useful for vacuum assisted biopsies, to prevent pneumothorax and to facilitate maximum tissue yield in very soft or non-texturized tissues.

specimen can be taken if necessary through the cutting cannula that remained in place. After the biopsy procedure a tissue marker is left in place in some (breast) patients, in particular for non-palpable lesions, to prove the exact site of the biopsy and to relocate the biopsy site for surgery. Finally the cutting cannula is removed, and a gently compression is applied at the biopsy site for about 2 minutes. Bleeding is subsequently verified by imaging immediately after the procedure.

For skin and endocavitary applications (gynecology), a similar approach is applied, using kits without trocar since the biopsy starts from the surface of the target area.

All procedures were performed in an outpatient setting and mainly in the consultation room, with or without nurse assistance and with minimal time delay between offering and performing the biopsy. For CT and MRI guidance, the patient was exclusively seen in the radiology department.

Biopsy specimens were immediately immersed in buffered 10% formaldehyde prior to instant shipment to the laboratory. In some cases, a mirror biopsy i.e. longitudinal cut of the specimen, was immersed in specified media such as ionic solutions for mRNA preservation. The vials were labeled identical with patient information and accompanied with thorough clinical and patient information in order to prevent mixing up materials and to provide the laboratory with essential clinical information. Complete pathological and biomolecular results were obtained after a maximum of 2 weeks with preliminary reports starting within 2 days. Various molecular tests can be considered in (immune-) histochemistry and homogenate based diagnostic platforms. All these tests were requested depending on the type of cancer. If there was any issue related to tissue harvest when a test was not possible, this procedure was considered non-successful (none of the cases).

Patients were seen post-procedural one or two weeks later for communicating the results, planning of molecular profiling, planning of follow-up, estimation of side effects and type complications seen. If pain had been noted, the degree was evaluated with the visual pain assessment score.

A successful biopsy was defined as absence of complications requiring reintervention, hospitalization or prolonged hospitalization, and sufficient material to allow all required histological (slide based) and molecular biology (homogenate based) investigations leading to an identical diagnosis as compared to subsequent surgery (n=458), or confirmation of non-malignancy. The pathology lab judged the tissue specimen pre-analytically. For specimen of inferior quality (target to sample ratio below 50%), the procedure was considered not successful (n=0). When multiple samples were taken during one procedure, all the samples had to contain at least 50% cancer cells to account for a successful procedure. For those patients that had no subsequent surgery and no malignancy on biopsy, a minimal follow-up time of 6 months with re-exploration was respected (n=451).

All relevant patient and biopsy data were recorded in an excel database; including dimensions of the biopsy (whenever available from lab), pathology and molecular biology data. Hard copies of the pathological/biomolecular report were collected and stored for verification purposes and to compare data from surgery with data from D&F biopsy.

The study used T-test for comparison of sample size. Descriptive statistics are provided in the remainder of the text because of the nature of data. For continuous measurements, the number of observations with non-missing data, means and standard deviations (SD) are presented. For categorical variables, the observed frequencies and percentages are reported.

RESULTS

During the inclusion period, 910 patients (92% female gender, age range 18-101y, predominantly Caucasian ethnical background) provided informed consent to enter the study. One patient collapsed before the biopsy attempt and was excluded from further participation. Twelve hundred and nine (1209) biopsies were taken in 909 patients according to the standardized procedure described in M&M section. One patient underwent two biopsies of the thyroid on two different periods of his disease: the first to confirm the diagnosis of primary thyroid lymphoma and the second to assess a clinical suspicion of recurrence. Another patient had two biopsies at the same time for suspicion of synchronic bilateral breast cancer. All others had one or more biopsies in the same organ in one procedure.

Virtually all anticipated sites of the human body could be sampled. The different sites were grouped in 9 areas and are presented in Table 1.

The largest group comprised biopsies of the breast, exclusively (n = 589). This reflects the mainstream of the department of oncology. All these applications were done under US guidance. The abdomen groups 19 patients with biopsies in the liver, peritoneum, kidney, and pelvis. All were done under CT guidance. Lymph nodes (n=117) from all peripheral stations were approached, mainly in the axilla, groin and neck region. Bone biopsies were performed for suspicious osteolytic areas (n=38), using US guidance whenever the lesions were visible, or alternatively with CT (n= 32) or MRI (2 patients). The gynecological applications (n =29) could be divided in cervical biopsies (n = 17), endometrial (n=2), vulva (n = 3), and vaginal biopsies (n = 7). As for the skin biopsies (n = 57), all gynecological biopsies were made under direct vision except for endometrial applications (intracavitary or abdominal US). Head & neck (non-lymph node) localizations (n = 26) were challenging because of the high vascularization and anatomical restrictions (e.g. short fat neck).Five of them were achieved under CT guidance, while US was used in the remainder. Eight were thyroid biopsies, 9salivary glands and 9 masses of unknown primary origin. All head & neck procedures were performed with a 8 or10 Gauge needle. Similarly, 28intra-thoracic biopsies were performed with an 8 to 10 Gauge needle, using CT assistance in the majority of peripheral lesions (n =17) and central lesions (n=7). Finally, 6 muscle biopsies were performed under US in various parts of the body.

Overall, malignant disease was diagnosed in 448 (49%) samples; while in 305 (33%) a benign condition was found. In 156 (17%) specimens no disease could be detected.

Efficacy data

Of 909 biopsy procedures using the D&F technique, 886 (97%)

Table 1: Overview of the number of biopsies and success rates according to site of biopsy.

Site of biopsy	Successful biopsies (n)	Total number of biopsies (N)	Success Rate
			%
Abdomen°	19	19	100
Lymph Node	109	117	93
Bone°	37	38	97
Breast	578	589	98
Gynecology	29	29	100
Head & Neck°	24	26	92
Thorax	27	28	96
Muscle	6	6	100
Skin	57	57	100
All sites	886	909	97

° Abdomen: includes liver and peritoneal masses,
° Bone applications were for osteolytic lesions,
° H&N: includes thyroid, salivary glands and non-lymph node solid masses.

were uncomplicated and resulted in high quality tissues leading to a diagnosis that was confirmed during subsequent surgery and follow-up. Success rate per organ area is summarized in Table 1.

Two biopsies were not successful due to procedural complications: in one a transthoracic biopsy was highly diagnostic, but the patient developed a pneumothorax; the other targeted a chronic and hard lymph node in the head and neck region of an 86 year-old lady, resulting in a small fragment of fibrotic tissue. This patient developed a large but self-limiting cervical hematoma, requiring hospitalization for 48 hours.

In 22 cases, the D&F approach resulted in harvest of non-representative tissues. Eight failures were from lymph nodes and occurred mainly in the first part of the study. All of them resulted from inappropriate visualization, anatomical constraints (head & neck) or were harvested from a region where at that time insufficient experience in transdermal sampling was available (e.g. pelvis). In one bone sample the pathology showed necrotic tissue while surgical debridation pointed towards sarcoma tissue. In 11 breast cases, biopsies were not diagnostic, or showed incomplete correlation between biopsy and surgery (n=7). For example, one lesion proved to be an invasive carcinoma whereas the transdermal biopsypointed towards ductular carcinoma in situ; similarly, two lesions were an invasive cancer at surgery, while the biopsy specimen suggested fibrocystic disease. Finally, two head & neck procedures missed the correct diagnosis, one showing fibromuscular tissue where surgery showed a poorly differentiated epithelial cancer and the other having been interruptedin a painful malignant parotid lesion due to unbearable pain during harvest.

A total of 1209 biopsy samples were harvested in 909 patients (1.33 per patient (range 1-14, SD 0.82). Sample length was available in 271 patients (12.3 mm; range 1.5-35 mm, SD 0.82), diameter in 234 (3.81 mm; range 1 – 7 mm, SD 5.2), and weight in 73 (160 mg (SD = 0.004).In a few patients (n= 14) a tru-cut biopsy was obtained for comparison's purposes and placed on the same slide (Figure 2a, 2b).

Reproducibility of the biopsy specimens was tested in a comparative way between the overall first sample take (average 3.8 mm, n=234) and second sample (average 3.6, n=20) with T statistics 0.59 (P= 0.55).

Safety data

As mentioned previously, one patient developed a large cervical hemorrhage. Otherwise, the type of hematoma usually seen at the skin level was mild and varied from almost no hematoma to a maximum area of 5 cm in diameter (breast applications). In some patients a hematoma at the deeper target site was noted. The largest was seen in the breast and measured 4 cm on MRI. Forty-seven patients with CT guided punctures (n = 52 – 90%) had no hematoma at the deeper biopsy site up to 15 min post procedure (Figure 2c).

One patient developed apneumothorax requiring hospitalization after deep lung biopsies with a 10 Gauge Spirotome; this patient could be discharged after 4 days.

Comfort was usually excellent and the procedure needed to be terminated rarely due to pain or bleeding. In the occasion where the patient experienced pain, this was usually addressed during the procedure by adding local anesthetics. In case the procedure had to be stopped with insufficient material, the procedure was classified as non-successful (included in the 23 patients in table 1).

Cost

Cost calculation of the procedure accounted for the materials, infrastructure and personnel. The system was available to the center with costs up to 170 Euro (all in one single use set). When the 20 minute lasting procedure could be performed under US guidance (80 Euro) in the consultation room (25 Euro) there were no additional costs. When CT or MRI had to be considered an extra 300 Euro should be considered for material and personnel.

DISCUSSION

D&F tissue acquisition as described in this study is part of the diagnostic work-up of patients with a suspicious tumor lesion. The technology, as for all other biopsy tools, does not

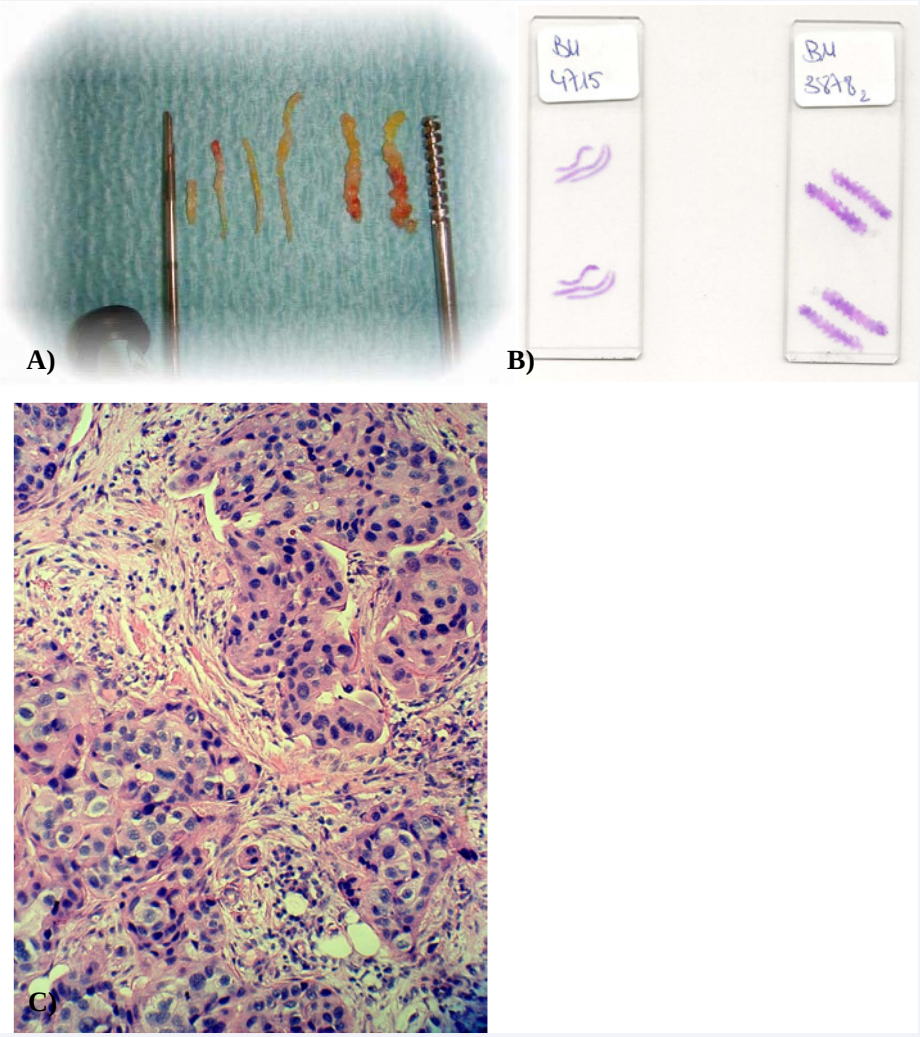

Figure 2 Comparison between tru-cut core needle biopsy and D&F specimen. 2a) Comparison between samples from a 14 Gauge tru-cut system (4 on the left – total weight 35 mg) and a 10 Gauge Spirotome (2 on the right – total weight 184 mg). Yellow tissue is fat, white tissue is fibrotic and red tissue contains cancer. **2b)** Paraffin Embedded fresh tissue slide from a tru-cut (left) and Spirotome (superficial cuts - right). **2c:** Microscopic view of a D&F specimen.

have therapeutic ambitions. Surgery for cancer, with curative intend, needs negative margins and these cannot be achieved with diagnostic sampling [17]. By study design, our series select patients with suspicious lesions scheduled for transdermal biopsy in a typical hospital, resulting in a large majority of female patients with breast cancer. The predominance of breast lesions may therefore influence the safety data, since hemorrhages in breast tissue rarely result in prolonged hospitalization, as opposed to e.g. higher-risk liver biopsies. In order to correct for this imbalance, the efficacy and safety data were studied in general and per grouped target site.

The D&F technique was highly successful in our experience with for example false negative rates (2%) comparable to tru-cut and vacuum assisted needles in the breast [10]. In areas where guidance was less appropriate (e.g. axillary or head & neck) some biopsy specimens turned out to be less representative of the target lesion. A similar phenomenon was noted in the breast where diffuse lesions were harvested in the most echographical suspect zones which are not always immediately related to the most invasive lesion (e.g. rather fibrosis could be seen instead of the invasive cancer). Moreover, a certain learning curve appears to play a role in successful tissue harvesting, since most unsuccessful tissue acquisitions where at the beginning of the study or when new indications were explored. For instance, most of the unsuccessful lymph node biopsies where found in the head & neck region where simultaneous ultrasound probe placement and biopsy was not ideal. Adaptation of the technique using dedicated smaller transducer guidance appeared to be much more accurate.

Severe peri-procedural complications, such as pain, pneumothorax, and bleeding, occurred in 0.2% only of D&F procedures in our series, including a pneumothorax during lung biopsy in one and a large cervical hematoma in another. Pneumothorax is a frequent complication of all transdermal procedures that cross the pleural cavity. Interestingly, according to most publications, FNAC (18G needles) results in similar

pneumothorax risks compared to tru-cut (14G needles) procedures, with rates reported between 20 and 30% [18-19], and between 10 and 30% [20-21], respectively. Intuitively, a higher complication rate can be expected with larger needle diameters [22], but not all available data point into the same direction [23]. In our experience with the 10G Spirotome, the rate of pneumothorax and bleeding for transthoracic punctures was as low as 3.5%, and compares favorably with other research groups using 14 G and 18 G needles [24,25]. One explanation is that the technology is quite different and the penetrating helix body in the target zone is about the size of an 18 G tru-cut needle. Moreover, the D&F macrobiopsy is performed to obtain tissue for molecular profiling and pathology and therefore should be compared with biopsies under thoracoscopic conditions. During thoracoscopy, the procedure inherently uses a iatrogenic pneumothorax mandating post procedure hospitalization. In contrast, with D&F macrobiopsies, a pneumothorax or bleeding is considered to be a complication, while most procedures are uneventful and avoid the need for hospitalization.

In terms of pain and pain control during D&F (breast) biopsies, the pain sensation of a regular mammography was quoted higher compared to the biopsy step itself, indicating in another way the comfort of this technology (data not shown) [26]. As compared with systems approaching tissues from the side, D&F biopsies take the advantage of penetrating the lesion frontally through a fully anesthetized tissue tract [27]. Indeed, local anesthetics are aqueous solutions that are used in predominantly fatty subdermal tissues, limiting their maximal effect to a cylindrical needle tract. In the core of this hypothetical cylinder the anesthesia is complete but the more the tissue uptake is remote from the central axis the less local anesthesia has been reached. For the same reason, repeat biopsies e.g. for removal of micro calcifications do not increase pain sensations [28]. In this indication, D&F technology appears to be less painful compared to vacuum-assisted biopsy [29].

As mentioned, the D&F technique was predominantly used in the work-up of breast lesions. We did, however, explore the potential of this biopsy technology in less accessible organs. So far, the thyroid was considered to be only accessible with FNAC [30], while tru-cut shooting systems are not considered useful in an organ with a thickness of less than 1 cm and endorsed with cartilage [31]. We used the Spirotome to harvest tissue specimens using 8 and 10G needles. In contrast to contemporary belief that the thyroid is extremely vulnerable to bleeding, we found that macrobiopsies of this organ are quite feasible. Given the diagnostic uncertainties with FNAC and the general attitude to refrain from surgery whenever possible [32], the D&F macrobiopsy provides an excellent alternative. Histology with the addition of biomolecular data offers new opportunities for better diagnosis and treatment [33].Similarly, the trans dermal approach using D&F technology can successfully be applied for head &neck tumor sampling. The good visibility of the helix and verification of the position of the helix before cutting makes the procedure safe in these highly vascularized areas, with 92% success rate in our experience. Attention should be paid to the right position of the needle before cutting to avoid non-representativity in the sample.

We performed a limited number of cases in muscle tissue, and our results compare favorably with the experience of other groups with regards to safety and efficacy. Harvest of muscle tissue may however become of paramount importance in tissue regeneration research and its clinical applications [34]. Within this regard, reliability of sample size and quality of tissue (number of living cells of interest) is important. The difference in sample size with the D&F is insignificant and pathological tests show transplantation quality (data not shown here).

While larger blood vessels in the immediate vicinity of lymph nodes make tru-cuts prone to bleeding, the D&F technology enables a safe cylindrical sampling of both the cortex and medulla, offering a valid diagnostic alternative to surgical sampling. The overall success rate in our series was 93%, despite several failed cases with poor visualization or at the beginning of our experience, making surgery for diagnosis of lymphoma rather second choice. The adagio that low grade lymphomas can only be diagnosed when the entire lymph node is resected does not hold in an era where molecular diagnostics can be applied to find monoclonality. The results are also better in lymph nodes with metastatic cancer. Epithelial cells are readily recognized but here again, the volume of the tissue and the representatively (volume of tumor cells in relation to contaminating lymphoid tissue) are essential in providing meaningful biomolecular and/or genetic data. One special feature of the D&F technology for lymph nodes is that the target (lymph node) can be grasped up by the helix point. Before cutting, the affected lymph node can be retracted from neighboring blood vessels and nerves and the cutting can be performed at a distance from these structures.

Of interest are the gynecological applications where the technology proved successful in addition to laparoscopic procedures [35]. Abdominal applications of D&F systems have been extensively studied in animals [36,37] as well as in humans [38]. Given the possibility to use the Spirotome under MRI guidance [39] and its high safety profile, transdermal tissue acquisition gradually replaces diagnostic surgery [40]. Primary and metastatic abdominal cancers are increasingly treated with targeted treatments making molecular biology an integral part of the diagnostic work-up [41].

With regards to intra-thoracic tissue sampling, the emergence of new therapeutic agents for non-small cell lung cancer (NSCLC) implies that histologic subtyping and molecular predictive testing are now essential for therapeutic decisions. Histologic subtype predicts the efficacy and toxicity of some treatment agents, as do genetic alterations, which can be important predictive factors in treatment selection. Similarly, molecular markers, such as epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement, are the best predictors of response to specific tyrosine kinase inhibitor treatment agents. As the majority of patients with NSCLC present with unresectable disease, it is therefore crucial to optimize the use of tissue samples for diagnostic and predictive examinations [42]. With proven efficacy and safety, transdermal procedures for tissue harvesting can now be considered the state-of-art with acceptable complication rates (pneumothorax).

Larger samples contribute to the quality of pathological examination and molecular biology, hereby avoiding costs related

to tests that don't contribute to personal diagnostics. External quality assurance programs are essential to guarantee optimal quality of testing for both pathology and molecular biology, ultimately saving costs. With regards to tissue acquisition, high quality tissue presents 4 main characteristics: sufficient tissue, high degree of purity, representativity and freshness. Inter-observer agreement between pathologists therefore increases with sample quality [43], and similar findings were seen in the evaluation of high-output biomolecular platforms [44].

The main finding of research on transdermal macrobiopsy technology is that diagnostic surgery can often be avoided, bringing personalized diagnostics and therapeutics closer to the cancer patient. In our series, surgery could be avoided in those patients were no malignancy was noted (33%), or in those where biopsies showed absence of pathologic tissues (17%). Together, 50% of the patients could avoid surgery because no malignancy was detected. Finally, only 312 patients, almost entirely breast cancer patients, underwent subsequent surgery (34%) bringing the percentage of patients that avoided surgery to 66%. On the other hand, some patients did undergo surgery for benign lesions, such as breast fibro adenomas or mixed tumors in the parotid gland.

On average, the cost of D&F technology adds 294 Euro per patient, a minor fraction of the cost of surgery. In addition, molecular biology testing averages 3500 Euro per patient. The costs of these tests are only acceptable if the data are contributive towards better treatment choices. Here the real value of high quality tissues is emerging. Finally, targeted therapeutics are extremely expensive (3000 Euro per patient per month for the medication is not unusual) and still increasing. The obvious challenge in modern oncology is how the declining financial resources will be optimally used. Better patient selection based on discriminative biomolecular testing is probably the only way to pursue. In this philosophy, optimal tissue acquisition is one of the most important cost-effective steps to consider.

CONCLUSION

With the addition of D&F macrobiopsy systems to harvest high quality tissues for molecular biology with increased comfort to the patient and operator at low complication rates and affordable costs to the health care system, personalized diagnosis and treatment is now available to almost every patient at any time during the course of the illness. In addition, other fields of research such as fertility and regenerative medicine where quality of tissue translates into percentage of living cells may profit from these novel technologies.

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Conflict of interest

None of the authors have any conflict of interest to mention except JJ. His wife is CEO of a Medical Device company MedInvents to which JJ was consultant during the study period. JJ is consultant for pharmaceutic and medical device companies.

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